No. 2025-1927

UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

NOVARTIS PHARMACEUTICALS CORPORATION, *Plaintiff-Appellant*

v.

MSN PHARMACEUTICALS INC., MSN LABORATORIES PRIVATE LIMITED, MSN LIFE SCIENCES PRIVATE LIMITED, *Defendants-Appellees*

Appeals from the United States District Court for the District of Delaware, Nos. 20-md-2930-RGA and 22-cv-1395-RGA, Judge Richard G. Andrews.

NOVARTIS PHARMACEUTICALS CORPORATION'S CONFIDENTIAL EMERGENCY MOTION FOR INJUNCTION PENDING APPEAL AND TO EXPEDITE THE MOTION

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JULY 14, 2025

CERTIFICATE OF INTEREST

Counsel for Novartis Pharmaceuticals Corporation certify under Federal Circuit Rule 47.4 that the following information is accurate and complete to the best of their knowledge:

1. **Represented Entities.** Provide the full names of all entities represented by undersigned counsel in this case.

Novartis Pharmaceuticals Corporation.

2. **Real Party in Interest.** Provide the full names of all real parties in interest for the entities. Do not list the real parties if they are the same as the entities.

None.

3. **Parent Corporations and Stockholders.** Provide the full names of all parent corporations for the entities and all publicly held companies that own 10% or more stock in the entities.

Novartis AG.

4. **Legal Representatives.** List all law firms, partners, and associates that (a) appeared for the entities in the originating court or agency or (b) are expected to appear in this court for the entities. Do not include those who have already entered an appearance in this court. Fed. Cir. R. 47(a)(4).

McCARTER & ENGLISH, LLP: Daniel M. Silver, Alexandra M. Joyce, Maliheh Zare.

SCHRADER COMPANION DUFF & LAW PLLC: Sandra K. Law, James F. Companion.

VENABLE LLP: Gregory J. Manas, Laura K. Fishwick, Melinda R. Roberts, Shannon K. Clark, Susanne L. Flanders, Whitney M. Howard, Carrie S. Park.

MORRISON & FOERSTER LLP: Deanne E. Maynard, Seth W. Lloyd, Rebecca W. Setrakian, Joel F. Wacks.

5. **Related Cases.** Other than the originating case(s) for this case, are there related or prior cases that meet the criteria under Fed. Cir. R. 47.5(a)?

Yes, see separately filed notice.

6. **Organizational Victims and Bankruptcy Cases.** Provide any information required under Fed. R. App. P. 26.1(b) (organizational victims in criminal cases) and 26.1(c) (bankruptcy case debtors and trustees). Fed. Cir. R. 47.4(a)(6).

Not applicable.

Dated: July 14, 2025 /s/ Jared L. Stringham

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CONFIDENTIAL MATERIAL OMITTED

In the non-confidential version of this brief, pages 21-22 omit material describing Novartis's confidential financial information.

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TABLE OF ABBREVIATIONS

ANDA	Abbreviated new drug application
API	Active pharmaceutical ingredient
cm^{-1}	Wavenumber
FDA	United States Food and Drug Administration
IR	Infrared spectroscopy
mg	Milligram
POSA	Person of ordinary skill in the art
ssNMR	Solid state nuclear magnetic resonance
TVS	Trisodium valsartan sacubitril complex

FEDERAL CIRCUIT RULE 8 STATEMENT

Pending this motion's resolution, Novartis Pharmaceuticals Corporation seeks an immediate administrative injunction against MSN's commercial manufacture, use, offer to sell, or sale within the United States or importation into the United States of MSN's ANDA products and then a similar injunction pending appeal.[1] MSN may receive final FDA approval as soon as 12:01 am July 16, 2025, and has represented that it intends to launch its generic products as soon as possible unless a court order prevents it from doing so.

Novartis thus needs relief before the end of the day July 15, 2025, because MSN seeks to market generic products that would compete with Novartis's ENTRESTO® drug before the expiration of Novartis's U.S. Patent No. 11,096,918. FDA initially approved MSN's ANDA in July 2024. But MSN has never launched because, in a related appeal involving Novartis's U.S. Patent No. 8,101,659, this Court granted an injunction pending appeal barring MSN from launching and ultimately upheld the validity of the '659 patent, which MSN had stipulated to infringing. *In re Entresto*, 125 F.4th 1090, 1100 (Fed. Cir. 2025). On remand, the district court ordered the effective date of MSN'S ANDA approval to be not earlier

[1] "MSN" refers collectively to MSN Pharmaceuticals Inc., MSN Laboratories Private Limited, and MSN Life Sciences Private Ltd. and, for purposes of the requested injunctive relief, their subsidiaries, agents, or affiliates.

than July 16, 2025, the day after the expiration of the pediatric-exclusivity period associated with the '659 patent. *In re Entresto (Sacubitril/Valsartan) Pat. Litig.*, No. 1:20-md-02930 (D. Del. Apr.1, 2025), ECF1824.

In this case, the parties tried the '918 patent in December 2024 , during which MSN withdrew its challenge to the patent's validity. On Friday, July 11, 2025, the district court issued its post-trial decision on noninfringement as well as its final judgment. Add1-24. That same day, it denied Novartis's motion for an injunction pending appeal based solely on the view that Novartis had not shown likely success on appeal "[f]or the reasons stated in the Trial Opinion." Add25.

Novartis notified MSN of this motion. MSN opposes. Novartis proposed to MSN that MSN respond within 4 business days (on July 19, 2025) with Novartis to reply within 1 business day (on July 22, 2025), but MSN indicated it needed more information on the issues Novartis would raise before responding on the schedule.[2]

[2] This appeal and Appeal No. 25-1928 arise from the same order and final judgment of noninfringement of the '918 patent, and so Novartis is filing this motion only in the lead appeal. *In re: Entresto (Sacubitril/Valsartan) Patent Litigation*, No. 1:20-md-02930-RGA, Dkt. Nos. 1938, 1939 (D. Del. July 11, 2025); *Novartis Pharms. Corp. v. MSN Pharms. Inc.*, No. 22-cv-1395-RGA, Dkt. Nos. 524, 525 (D. Del. July 11, 2025). Novartis's notice of appeal from that order and judgment was docketed in the district court in the dockets for both the MDL and the Civil Action case, per instructions from the District of Delaware, giving rise to two separate appeal numbers for the same appeal. *In re: Entresto (Sacubitril/Valsartan) Patent Litigation*, No. 1:20-md-02930-RGA, Dkt. No. 1940 (D. Del. July 11, 2025); *Novartis Pharms. Corp. v. MSN Pharms. Inc.*, No. 22-cv-1395-RGA, Dkt. No. 526 (D. Del. July 11, 2025).

INTRODUCTION

The Court should maintain the status quo pending appeal by enjoining MSN's generic ENTRESTO® products before the end of day July 15, 2025. Novartis scientists created a lifesaving heart-failure treatment: a new pharmaceutical combination of two drugs, valsartan and sacubitril. Sold as ENTRESTO®, the combination has become the preferred first-line treatment for certain types of heart failure—and Novartis's top-selling drug. Novartis devoted substantial resources to creating and growing a new market for ENTRESTO®, ultimately winning over physicians and patients who now recognize ENTRESTO®'s benefits. No generic versions of ENTRESTO® have ever been on the market. Yet MSN wants to capitalize on Novartis's success by launching more than a year before the '918 patent expires, forever disrupting ENTRESTO®'s market. Having abandoned its validity challenges, MSN seeks to launch before this Court resolves the substantial issues Novartis's appeal will raise about MSN's infringement. Such a launch would destroy this Court's ability to grant Novartis full relief following a successful appeal.

The Court should act now to prevent that result because Novartis's appeal is highly likely to succeed. The district court made at least one critical error: its decision hinges on a witness, Dr. McCreery, who lacks ordinary skill in the art. The parties agreed about the necessary level of skill: "'a person with a Ph.D. in chemistry or related field and two or more years of experience with solid forms of

pharmaceutical compounds, such as synthesizing, crystallizing, and characterizing solid forms of pharmaceutical compounds.'" Add4-5. Yet the district court acknowledged that Dr. McCreery lacks the requisite experience with solid forms of pharmaceutical compounds and thus is not a person of ordinary skill in the art. When others have similarly relied on such an unqualified witness for infringement, this Court has not minced words about the error: "'admitting testimony from a person with no skill in the pertinent art serves only to cause mischief and confuse the factfinder.'" *Kyocera Senco Industrial Tools v. ITC*, 22 F.4th 1369, 1377 (Fed. Cir. 2022) (alterations and citation omitted).

That is exactly what happened here. Although Dr. McCreery lacked experience with complexes and other pharmaceutical solid forms, his testimony was the linchpin of the district court's conclusion that Novartis's evidence was insufficient to distinguish whether MSN's ANDA products contain one solid form (an infringing amorphous complex) instead of another (a non-infringing amorphous physical mixture). The district court purported to credit Dr. McCreery's testimony over the testimony of Dr. Park, who has 25 years' experience characterizing pharmaceutical solid forms—including amorphous complexes—and runs a professional laboratory dedicated to pharmaceutical characterization services. The district court compounded its error by striking out on its own to reach conclusions on highly technical issues that neither the parties nor their experts advocated. This

was not a "battle" between two qualified experts; instead, the district court improperly accepted the testimony of MSN's witness who it acknowledged is not an ordinarily skilled artisan on key infringement findings that this Court should reverse.

Every other injunction factor also favors maintaining the status quo. Introducing a generic ENTRESTO® competitor will inflict massive financial damage on Novartis. That damage will be irreparable, permanently eroding ENTRESTO®'s price and causing incalculable losses. The public interest will also suffer, including the strong interest in honoring the bargain of disclosure for a limited patent term and in protecting this Court's ability to grant meaningful relief.

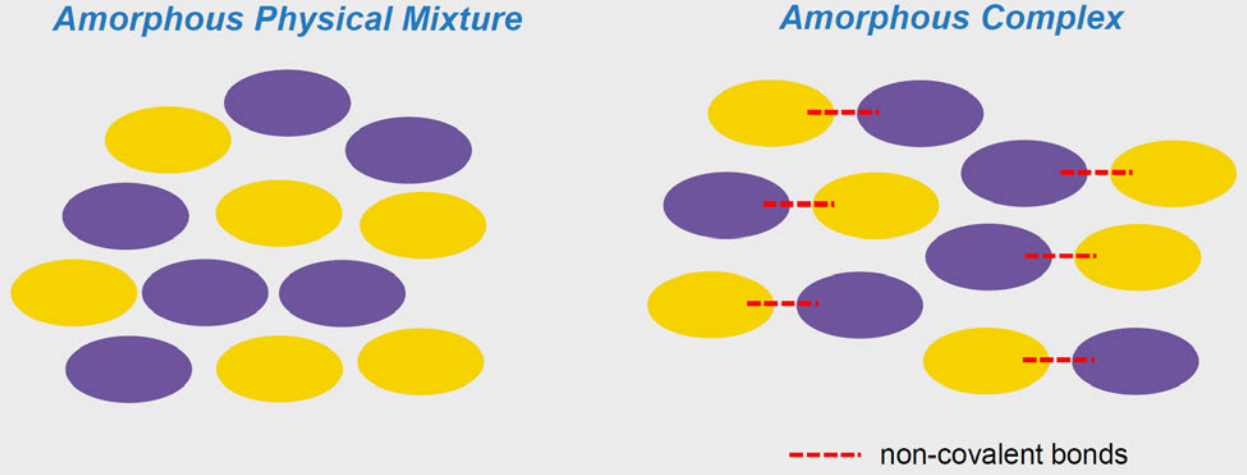
The Court should immediately enjoin MSN pending this motion's resolution and then pending appeal.

BACKGROUND

A. The '918 Patent Claims an Amorphous Trisodium Valsartan-Sacubitril Complex

After creating the foundational combination of valsartan and sacubitril claimed in the '659 patent, separate Novartis scientists built on that breakthrough. The '918 patent claims a novel "amorphous solid"—a "dual-acting compound" or "complex" of valsartan and sacubitril where units of the complex are arranged irregularly, rather than in a crystalline form with a repeating pattern. Add35(col.6:48-61); Add388-389(477:22-478:4). As illustrated below, an

amorphous complex differs from an amorphous physical mixture by the presence of non-covalent bonds linking the valsartan and sacubitril molecules:



See Add6 (district court recognizing same). The '918 patent claims an amorphous valsartan-sacubitril complex called Trisodium Valsartan Sacubitril, or "TVS," in which anionic valsartan, anionic sacubitril, and sodium cations are non-covalently bound in a 1:1:3 molar ratio. Add48(col.32:41-46); Add286(375:11-16); Add387(476:1-15). Such a complex structure is "beneficial over" "simply physically mixing the two active agents" for "use as first line therapy, ease of formulation, and ease of manufacture." Add41(col.17:46-51); Add46(col.28:27-32).

The '918 patent claim 1 recites:

> 1. An amorphous solid form of a compound comprising anionic [valsartan], anionic [sacubitril][3], and sodium cations in a 1:1:3 molar ratio.

Add48(col.32:42-46); Add386-388(475:21-477:21); Add286(375:19-376:16). The patent expires after November 8, 2026. Add26.

The patent describes ways to distinguish the TVS complex from a non-complexed physical mixture of sacubitril and valsartan, including with infrared ("IR") spectroscopy, solid-state nuclear magnetic resonance ("ssNMR") spectroscopy, and Raman spectroscopy. Add41(col.17:46-58); Add288(377:4-22). Raman spectroscopy involves scattering laser light off a substance to generate a Raman "spectrum" showing the intensity at different scattered energies, generally plotted in cm^{-1} (also called wavenumbers). Add629(718:8-24); Add296(385:11-23); Add5. Because the specific bonds in the substance cause the scattering, the peaks and other characteristics in a Raman spectrum are unique to the substance and can act "as a fingerprint" to identify it. Add296-297(385:24-386:5); Add630(719:19-24); Add740(829:19-24); Add5. Matching the Raman spectrum from an unknown compound to a reference Raman spectrum of a known compound can thus identify

[3] The chemical names recited in claim 1, "(S)-N-valeryl-N-{[2'-(1H-tetrazole-5-yl)-biphenyl-4-yl]-methyl}-valine" and "(2R,4S)-5-biphenyl-4-yl-4-(3-carboxy-propionylamino)-2-methyl-pentanoic acid ethyl ester" refer to valsartan and sacubitril, respectively. Add40(col.16:40-17:45); Add287-288(376:19-377:1).

the unknown compound, and can be used to distinguish different compounds. Add5-6; Add404-410(493:13-499:5).

B. Novartis Sued MSN for Infringement

Novartis sued MSN for '918 patent infringement after MSN sought approval to market generic ENTRESTO®. Add52-53.

1. Denial of preliminary relief

When FDA initially approved MSN's ANDA in mid-2024, the district court denied Novartis a preliminary injunction. Add207-217. This Court affirmed, but without reaching the grounds appealed here or irreparable harm. *Novartis Pharms. Corp. v. MSN Pharms.*, 2024 WL 4969281, at *5 (Fed. Cir. Dec. 4, 2024).

2. Post-trial judgment on validity and noninfringement

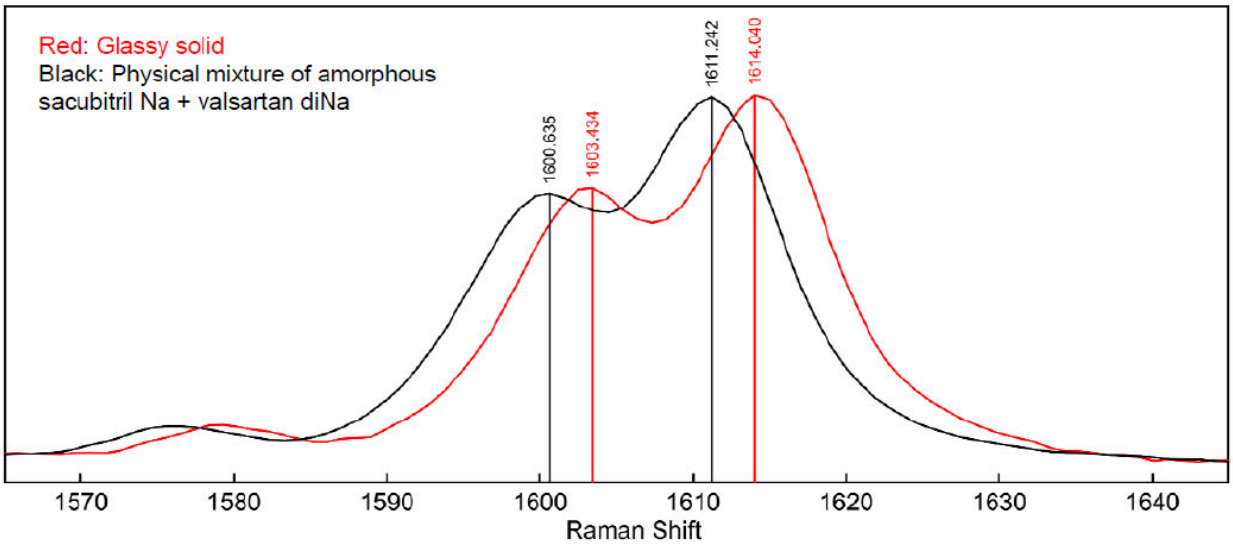
A December 2024 bench trial was held on infringement and validity. Before trial, Novartis moved to exclude Dr. McCreery's testimony, which Novartis renewed at trial. Add218-244; Add245-252; Add628(717:8-21); *see* Add1103-1104 (Novartis's post-trial brief renewing same). Nearing the trial's end, MSN abandoned its invalidity challenge "based on the Court's comments" that the challenge was "incredibly weak." Add946(1035:5-21); Add4. The post-trial decision addressed only infringement, focusing on Raman spectra. Add4-19.

a. Novartis's evidence from skilled artisans

Novartis relied on Dr. Park, an expert with 25 years' experience testing and characterizing solid-state pharmaceuticals, including complexes. Add282-283(371:8-372:1); Add1190-1194. Dr. Park runs a professional laboratory dedicated to that work and has "characterized a supramolecular complex and distinguished it from a physical mixture" "[m]ultiple hundreds of times." Add282-283 (371:8-372:1). Dr. Park followed the '918 patent's Example 1 to create the "glassy solid" amorphous TVS and measured its Raman spectrum for use as a reference. Add283-284(372:16-373:19); Add307(396:1-18); Add147(897:11-19). Dr. Park used a regularly calibrated, commercial Raman instrument to generate 256 scans of the glassy solid and average the results. Add322-326(411:10-415:25).

The resulting Raman spectrum showed several key differences compared to a spectrum of an amorphous physical mixture of valsartan disodium and sacubitril sodium. Add320(409:1-14). For example, Dr. Park found peak shifts in varying amounts (e.g., 5.7 cm^{-1}, 3.8 cm^{-1}, and 2.8 cm^{-1}), including the shifts shown below "in the carbonyl region," which had been shown in the art to be associated with "the formation of intermolecular hydrogen bonding," i.e., non-covalent bonds

Dr. Park's Raman Spectra for the Glassy Solid of Example 1 (Red) and Physical Mixture (Black) (1570-1640 cm^{-1} region)



Add305-306,320(394:15-395:14, 409:1-14); Add1195-1197. These changes in the Raman spectrum indicated the glassy solid differed from a physical mixture and was evident to her, as an ordinarily skilled artisan, that the solid was amorphous TVS. Add307(396:1-18). Dr. Park performed other testing, including ssNMR and IR testing, which confirmed the glassy solid was amorphous TVS. Add307(396:1-18). A second expert, Dr. Matzger, then matched Dr. Park's glassy solid Raman spectrum to Raman spectra obtained from MSN's products and identified the presence of infringing amorphous TVS in those products. Add406-410(496:23-499:5); Add1200-1204, 1209.

b. District court's reliance on a person unskilled in the art

The district court agreed with Novartis that Dr. Park's glassy solid was amorphous TVS. Add8(n.7), 16. It found "no reason to doubt Dr. Park's testimony

that [her company] followed Example 1 as faithfully as possible," and found MSN had failed to raise any challenge to Dr. Park's non-Raman tests "show[ing] that her glassy solid is amorphous TVS." Add8(n.7), 16.

Nevertheless, the district court questioned whether Dr. Park's Raman spectrum from the glassy solid could be used as an appropriate reference to prove that MSN's products contain amorphous TVS rather than a physical mixture—primarily by relying on Dr. McCreery's testimony. Add7-19. The district court acknowledged Novartis's unrebutted evidence that Dr. McCreery is not a person of ordinary skill in the art because he lacks experience with solid forms of pharmaceutical compounds, including characterizing complexes. Add7(n.5). But the district court reasoned it could still rely on Dr. McCreery's "opinions about Raman spectroscopy," calling them "not POSA opinions." Add7(n.5).

The district court proceeded to rely on Dr. McCreery's non-skilled-artisan views about characterizing complexes and other solid forms of pharmaceutical compounds. Add12-17. For example, adopting Dr. McCreery's view that Dr. Park's glassy solid Raman spectrum contained a "systematic shift" of 3 cm^{-1} compared to the spectrum for an amorphous physical mixture, the district court accepted Dr. McCreery's conclusion that it was "impossible" for the observed shift to result from "the bonds and molecular interactions present in an amorphous complex that are not present in an amorphous physical mixture." Add13. The district court also

purported to "credit Dr. McCreery's testimony" about what evidence would be needed "to conclude the two materials are in fact different," referring to the two different solid forms: infringing amorphous TVS versus a non-infringing amorphous physical mixture. Add17.

In so concluding, the district court identified no explanation for the different peaks in Dr. Park's Raman spectrum for the glassy solid beyond the one Dr. Park gave based on her decades of experience—they revealed the glassy solid was amorphous TVS and not an amorphous physical mixture. The district court did "not doubt the accuracy of the calibration tests conducted on Dr. Park's Raman instrument." Add16. Yet based on Dr. McCreery's non-skilled-artisan testimony, as supplemented by the district court's own interpretation of other limited evidence, the district court concluded MSN had "sow[ed] doubt" about the reliability of Dr. Park's glassy solid reference spectrum, leading the court to find noninfringement without addressing Novartis's infringement evidence comparing that reference spectrum to Raman spectrum from MSN's ANDA products. Add5-19.

In addition, even though MSN never "sought production of Dr. Park's glassy solid," the district court applied an adverse inference against Novartis for not producing a glassy solid sample to a different defendant, Noratech, that had settled. Add19, 21. The district court inferred that "had Novartis produced the glassy solid sample to Defendants, it would have been unfavorable to Novartis' case." Add22.

The district court did not cite the adverse inference as a basis for any of its determinations about the supposed reliability of Dr. Park's glassy solid reference spectrum. Add22.

Based on its trial opinion, the district court entered final judgment of noninfringement, also dismissing MSN's validity counterclaim with prejudice. Add23-24.

ARGUMENT

All factors favor enjoining MSN to prevent the commercial manufacture, use, offer to sell, or sale within the United States or importation into the United States of its ANDA products pending this appeal. 35 U.S.C. §271(e)(4)(B); 35 U.S.C. §283. Novartis has a strong likelihood of prevailing in setting aside the district court's noninfringement judgment on appeal given multiple reversible errors. Unless this Court maintains the status quo, Novartis will suffer immense and irreparable harm. The public interest favors protecting the patent bargain and ensuring this Court can grant meaningful relief. *Standard Havens Prods. v. Gencor Indus.*, 897 F.2d 511, 512 (Fed. Cir. 1990).

I. NOVARTIS WILL LIKELY SUCCEED ON APPEAL

A. The District Court's Decision Must Be Set Aside Because It Depends on Testimony from a Witness Lacking Ordinary Skill in the Art

When a witness lacks ordinary skill in the art, a court abuses its discretion by admitting that witness's "testimony on any issue that is analyzed through the lens of an ordinarily skilled artisan." *Kyocera*, 22 F.4th at 1377-78 (applying rule in reviewing ITC determination); *Sundance v. Demonte Fabricating*, 550 F.3d 1356, 1361-62 (Fed. Cir. 2008) (same reviewing district-court decision). Infringement is one such issue, as it is "analyzed in great part from the perspective of a person of ordinary skill in the art," making "technical evidence from that perspective" of "great utility." *Sundance*, 550 F.3d at 1361-62. Without that skill, "witness' opinions are neither relevant nor reliable." *Kyocera*, 22 F.4th at 1377 ("'cause mischief'"; "'advocacy from the witness stand'"). Thus, "[t]o offer expert testimony from the perspective of a skilled artisan" about infringement, a witness "must at least have ordinary skill in the art." *Id.* at 1376-77.

Dr. McCreery lacks that bare minimum and is not a person of ordinary skill in the art, as Novartis objected, before, at trial, and after. *Cf.* Add4-5 (accepted definition of skilled artisan). He has never personally tested any pharmaceutical compound by Raman spectroscopy; he "ha[s]n't studied supramolecular complexes," the '918 patent's subject matter; and he does not purport to have at least

two years' experience with solid forms of pharmaceutical compounds, or any experience characterizing complexes. Add655-659(744:1-748:7). The district court itself found Dr. McCreery's lack of relevant experience unrebutted. Add7(n.5). That lack of experience required the district court to exclude Dr. McCreery's testimony or, at the very least, shows clear error in its noninfringement determination, which relied throughout on Dr. McCreery's testimony. *Kyocera*, 22 F.4th at 1377-78; *Sierra v. Sisvel*, 130 F.4th 1019, 1024-25 (Fed. Cir. 2025) (similar).

The precedent requiring that outcome cannot be sidestepped by characterizing reliance on Dr. McCreery as only for "not POSA opinions." Add7(n.5). *Kyocera* rejected a similar attempt to rely on a non-skilled-artisan technical expert's opinions for some aspects of an infringement analysis but not others, there for literal infringement but not doctrine-of-equivalents infringement. 22 F.4th at 1377-78. This Court held that "[t]he absence of relevant knowledge and the risk for abuse apply equally to both situations." *Id.*

The same is true here given how the district court relied on Dr. McCreery. Among other things, the district court relied on his unqualified, non-skilled-artisan views about (1) whether "the bonds and molecular interactions present in an amorphous complex that are not present in an amorphous physical mixture" could explain the Raman spectra shifts Dr. Park observed (Add13); (2) whether more

testing would be needed "to determine if th[e] small differences" in Raman spectra "are significant enough to conclude the two materials are in fact different" solid forms of the pharmaceutical valsartan-sacubitril combination (Add17); and (3) what conclusions about amorphous TVS could be drawn from another reference, Redenti, comparing the Raman spectra of a different amorphous complex and a different physical mixture (Add12-14). Those highly technical opinions are all tied to experience with complexes and other pharmaceutical compound solid forms, the experience Dr. McCreery lacks. Add12-17.

Moreover, Dr. McCreery's non-skilled-artisan testimony that the district court accepted goes to issues that must be analyzed through the skilled-artisan lens, which Dr. McCreery was not qualified to do. The whole point of Dr. Park's Raman spectra was to produce an amorphous TVS reference to prove infringement, which is "exclusively determined from the perspective of ordinary skill in the art." *Sundance*, 350 F.3d at 1361-62. In repeatedly invoking the language of "reliability," the district court overlooked what that reliability was about—whether a skilled artisan in this field would conclude that Dr. Park's glassy solid Raman spectrum reliably reflected, and thus could act as a reference for, what she had produced: amorphous TVS, i.e., an infringing compound. Add12-17. Only a person possessing at least ordinary skill is qualified to testify about those issues. *Sundance*, 350 F.3d at 1361-62.

The district court's error in admitting and relying on Dr. McCreery alone shows Novartis's likely appellate success. Almost the entirety of its infringement analysis involved accepting Dr. McCreery's non-skilled-artisan testimony over Dr. Park's. Add7-17. Although the district court also briefly pointed to evidence about Novartis's "amorphous LCZ-696" compound, even then the district court relied on Dr. McCreery and never suggested that any evidence about "amorphous LCZ-696" could alone defeat infringement. Add17-19. Similarly, the district court was express that its "adverse inference" only supported noninfringement when "combined with" its conclusions based on Dr. McCreery. Add22.

B. Even Considering Dr. McCreery's Testimony, the District Court Clearly Erred in Reaching Conclusions Divorced from the Parties' and Experts' Views

The district court clearly erred regardless of Dr. McCreery's lack of experience in the art. The record does not support that Dr. Park's Raman spectrum of the glassy solid "is unreliable" (Add16), and setting aside that finding unravels the court's noninfringement determination.

First, the unreliability finding conflicts with the court's separate finding that Dr. Park proved the glassy solid is amorphous TVS, including by showing that the solid was made by "faithfully" following the patent's teachings and that independent "ssNMR and IR spectra tend to show that her glassy solid is amorphous TVS." Add8(n.7), 16. Neither MSN nor Dr. McCreery explained how the glassy solid

could produce the distinct Raman spectrum Dr. Park measured other than that the glassy solid is amorphous TVS, as the ssNMR and IR spectra showed. Instead, they argued that the glassy solid produced Dr. Park's Raman spectrum because the solid was an amorphous physical mixture. Add1137-1152; Add638-641,647-648. Although the district court thought there was enough to "sow doubt" about the Raman spectrum (Add16), it had no basis for relying on its own unsupported speculation on such a technical issue. *Centricut v. Esab Grp.*, 390 F.3d 1361, 1369-70 (Fed. Cir. 2004) (reversing infringement determination based on "district court's own interpretation" of "complex technology").

Second, the district court misstated and misunderstood Dr. McCreery's testimony. For example, the district court stated Dr. McCreery "would have conducted further testing to ensure that *the two spectra* were in fact different," meaning the spectrum from the glassy solid and that from the physical mixture. Add15(emphasis added; citing Add649(738:9-13). Dr. McCreery actually said he would have done more testing to determine whether there are different *compounds*, and whether the glassy solid Raman spectrum shows "a new compound" or an amorphous physical mixture. Add649(738:9-13). The district court's misdescription matters because Dr. Park performed additional testing, including ssNMR and IR testing, that confirmed the glassy solid is a different compound: amorphous TVS, as the district court itself found. Add16.

Third, the district court clearly erred in its reliance on the Redenti article and "amorphous LCZ-696" evidence. MSN and Dr. McCreery insisted that because Redenti showed differences besides peak shifts between the spectra of a different amorphous complex and a different amorphous physical mixture, such differences were required to conclude Dr. Park's glassy solid is not a physical mixture. Add641-642(730:11-731:17). For starters, the district court overlooked that Dr. Park and Dr. McCreery agreed that Redenti's Raman spectrum would not be the same as that expected for amorphous TVS because the complex there, piroxicam-β-cyclodextrin, is structurally different from amorphous TVS and thus would show different Raman spectrum features. Add344-345(433:9-434:4); Add668(757:10-758:3). Regardless, given the other evidence—credited by the district court—showing Dr. Park's glassy solid is not a physical mixture but amorphous TVS, Novartis had no need to identify other differences in the Raman spectra. Add16.

Similarly flawed is the district court's speculation that "there is a reasonable likelihood that amorphous LCZ-696 is amorphous TVS." Add17-19. The court thought an unexplained slide in an internal Novartis presentation referencing "amorphous-LCZ696" could be a Raman spectrum of amorphous TVS and thus could cast doubt on the reliability of Dr. Park's Raman spectrum. Add17-19. But no technical witness testified that the "amorphous LCZ-696" spectrum was amorphous TVS. Indeed, Dr. McCreery agreed that "whatever amorphous LCZ is

in the Pan presentation, that's not the glassy solid material from the '918 patent" because "[t]he spectrum is different." Add673(762:2-10); Add341-342(430:7-431:25) (Dr. Park; similar). MSN never argued that Dr. Park's glassy solid, which the district court found is amorphous TVS, and "amorphous LCZ-696" are both amorphous TVS, as the district court suggested. Add17-19. Instead, the court again adopted conclusions at odds with both parties, all technical witnesses, and the record. This too shows clear error.

C. The District Court's Flawed Adverse Inference, Related to Discovery MSN Never Requested, Cannot Help MSN's Appellate Chances

Although the district court also imposed an adverse inference that "had Novartis produced the glassy solid sample to Defendants, it would have been unfavorable to Novartis's case," that inference cannot defeat Novartis's likely appellate success, as the court never suggested it sufficed to support noninfringement. Add22("combin[ing]" inference with other findings). Novartis is also likely to show that imposing a sanction in favor of MSN was an abuse of discretion based on "an erroneous view of the law" and "a clearly erroneous assessment of the evidence." *Drone Techs. v. Parrot S.A.*, 838 F.3d 1283, 1297 (Fed. Cir. 2016) (applying Third Circuit law; citation omitted).

As an initial matter, Noratech—a different defendant—was the only party that requested Dr. Park's glassy solid, as the district court acknowledged.

Add1016(1104:3-12). It was simply too late when, for the first time at trial, MSN complained about discovery it never sought. The district court was clearly wrong in describing this as a "common" discovery dispute. Add21.

Furthermore, in Dr. Park's May 9, 2024 expert report, Novartis timely disclosed to both Noratech and MSN the existence of her glassy solid sample and all related data. Following that disclosure, neither defendant requested nor moved to compel production of the glassy solid sample, which Dr. Park continued to possess. Noratech instead waited until the eve of trial and sought an adverse inference. Such strategic behavior should not warrant an adverse inference even for Noratech, particularly given that the district court itself considered Novartis merely to have made "some discovery mistake" without bad faith. Add1016(1104:3-12); Wright & Miller, 8B Fed. Prac. & Proc. Civ. §2289 (3d ed.) ("failure to move for sanctions in a timely fashion may preclude a belated request").

Regardless, Federal Rule of Civil Procedure 37(c)(1), on which the district court relied, prohibits sanctions for a failure that "is harmless." For MSN, the district court's own findings show harmlessness. MSN never requested Dr. Park's glassy solid, never moved to compel its production, and thus never itself sought to develop challenges about it during discovery.

Even when MSN belatedly sought the benefit of any sanction granted Noratech, MSN merely requested an adverse inference that testing the glassy solid

would have shown it "w[as] not amorphous TVS or distinguishable from a physical mixture." Add1168. Yet the district court found that the entirety of the record evidence, including Dr. Park's non-Raman testing, showed the glassy solid *is* amorphous TVS. Add8(n.7), 16. That finding dispels the only harm MSN alleged. Indeed, that MSN suffered no harm is confirmed by the district court's failure to specify any particular adverse inference—as it had already rejected on the facts the inference MSN sought.

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Any of these errors suffices to show Novartis's strong likelihood of success on appeal. Combined, they compel preserving the status quo.

II. NOVARTIS WILL SUFFER IRREPARABLE HARM ABSENT AN INJUNCTION

MSN's threatened at-risk launch will cause Novartis immediate irreparable harm. Novartis will suffer a dramatic loss of market share, lose substantial profits, and ENTRESTO®'s price will irreversibly erode. These are classic harms that support preserving the status quo pending appeal.

A. An MSN Launch Will Irreparably Crater ENTRESTO®'s Market and Upend Novartis's Market Position

"Evidence of head-to-head competition and lost market share can support a showing of irreparable harm." *Natera v. NeoGenomics Lab'ys*, 106 F.4th 1369, 1378 (Fed. Cir. 2024). So can evidence that "the alleged injury is not quantifiable."

Id. This Court thus has recognized the harm, often irreparable, of forcing a patentee to compete against an infringer in a market the patentee "created with its investment in patented technology." *Douglas Dynamics v. Buyers Prods.*, 717 F.3d 1336, 1344-45 (Fed. Cir. 2013).

Novartis's substantial investments in ENTRESTO® created a new market, making ENTRESTO® Novartis's top-selling drug. Add1212, Add1214(¶¶3-4, 11). That new market has generated over $4 billion in U.S. sales in 2024 and continues to expand. Add1212, Add1214(¶¶3-4, 11); Add1328-1330, Add1333-1336, Add1344-1346(¶¶27, 58-62, 67-72, 89-92). ENTRESTO® is Novartis's highest-earning brand and Novartis uses profits from ENTRESTO® to fund research and development for new patient therapies. Add1212(¶4).

An at-risk launch will crater this market and destroy Novartis's position in it. Generic entry "cause[s] notable decreases" in the branded drug's sales, "almost always lead[ing] to an immediate reduction." Add1310(¶22). The effects on ENTRESTO® would be catastrophic. Within a month of launch, ENTRESTO® sales would plummet to less than [redacted] of the sales that would occur without a generic launch. Add1314(¶28). Total lost sales would exceed [redacted] one year after a generic entry. Add1314-1315(¶¶28-31).

These harms will be irreparable. *First*, there will be no coming back from the price erosion an at-risk launch would cause. Large third-party payers—private

insurance plans, managed care organizations, and Medicare—account for most prescription-drug spending; "[t]he presence of a generic competitor in the marketplace, even briefly, would likely fundamentally shift customer pricing expectations and strengthen the negotiating leverage of institutional purchasers." Add1321, Add1337-1342, Add1351-1355(¶¶42, 76-85, 103, 106-108). This pressure would likely force Novartis into immediately [redacted] for its Medicare contracts, which "[redacted]. Add1341, Add1354(¶¶83, 107). This Court has recognized the irreparable harm from irreversible price erosion and loss of goodwill caused by an infringing generic competitor. *Abbott Lab'ys v. Sandoz*, 544 F.3d 1341, 1361-62 (Fed. Cir. 2008); *Sanofi-Synthelabo v. Apotex*, 470 F.3d 1368, 1382 (Fed. Cir. 2006).

Second, the total damage is unquantifiable. Entresto's patient base continues to expand, and even Novartis has consistently under-forecasted ENTRESTO®'s net revenues. Add1344-1346(¶¶89-92). That dynamic reflects increased demand driven by recent clinical trials and updated clinical guidelines. Add1333-1336(¶¶67-72). Any lost-profits calculation would thus be difficult and likely understate Novartis's actual damages. Add1333-1355(¶¶66-109); *see Celsis in Vitro v. CellzDirect*, 664 F.3d 922, 930-31 (Fed. Cir. 2012) (irreparable harm based on difficult-to-quantify losses); U.S. Statement of Interest at 9-15, *Radian Memory v. Samsung Elecs.*, No.

2:24-cv-01073 (E.D. Tex. June 24, 2025) (difficulty in calculating patent-infringement damages supports irreparable harm).

Third, MSN has not contested that 35 U.S.C. §271(e)(2) provides a proper basis for Novartis's infringement claim. As a mandatory remedy for §271(e)(2) infringement—without any equities showing—Congress requires an order resetting an ANDA approval to no earlier than patent expiration. 35 U.S.C. §271(e)(4)(A); *Vanda Pharm. v. West-Ward Pharm. Int'l*, 887 F.3d 1117, 1138 (Fed. Cir. 2018). MSN's at-risk launch would render that relief all-but worthless, further demonstrating Novartis cannot be made whole after the judgment.

B. MSN's Infringement Would Cause Novartis's Harm

The irreversible harm from an at-risk launch will be the result of MSN's infringement. The causal nexus analysis is "flexible." *Apple v. Samsung Elecs.*, 809 F.3d 633, 641-642 (Fed. Cir. 2015). Where (as here) the irreparable harm stems from competition with an infringing product, the patentee need only "show 'some connection' between the patented features and the demand for the infringing products" (*id.* at 642), not that the infringing features are "the exclusive or predominant" cause of the harm. *Genband US v. Metaswitch Networks*, 861 F.3d 1378, 1383 (Fed. Cir. 2017) (quotation marks and emphasis omitted).

That standard is more than satisfied here. The manufacturing process for MSN's generic products, specifically the coating step, invariably leads to the

presence of amorphous TVS, the infringing compound. Add402-403, Add443(491:13-492:6, 532:4-14). MSN must follow that process, including because MSN's ANDA described it to FDA. *See Abbott Laby's v. TorPharm*, 300 F.3d 1367, 1373 (Fed. Cir. 2002). So MSN cannot make its products or launch at-risk without infringing.

That easily shows "some connection" between the infringement and Novartis's harm. *Apple*, 809 F.3d at 641. This Court has held that a patentee demonstrates causal nexus when infringement is a prerequisite to offering the feature that drives demand. In *Natera*, the Court concluded that an unclaimed feature—"highly sensitive tumor-informed testing"—drove demand, and that the feature was "impossible to achieve without" infringement. 106 F.4th at 1380. That sufficed to "tie[]" consumer demand (and thus the patentee's harm) to the infringement. *Id.* So too here, where MSN cannot make its generic competitor without infringing.

Nor does it matter that ENTRESTO® does not contain amorphous TVS. "In multiple instances, this [C]ourt has held that a party that does not practice the asserted patent may still receive an injunction when it sells a competing product." *Trebro Mfg. v. FireFly Equip.*, 748 F.3d 1159, 1171 (Fed. Cir. 2014) (collecting cases); U.S. Statement of Interest at 9-15, *Radian*, No. 2:24-cv-01073 (similar). Similarly, that the '918 patent is not Orange-Book-listed for ENTRESTO® does not defeat Novartis's irreparable-harm showing. This Court has upheld an irreparable-

harm finding and preliminary injunction barring sales of an infringing generic even though the infringed patent was not Orange-Book-listed. *Glaxo Grp. v. Apotex*, 376 F.3d 1339, 1344-45 (Fed. Cir. 2004); *Glaxo Grp. v. Apotex*, 64 F. App'x 751, 756 (Fed. Cir. 2003). MSN could have chosen a different manufacturing process that might have avoided infringement but did not. MSN must accept the consequences of its infringement.

III. THE EQUITIES FAVOR AN INJUNCTION

The equities and public interest also favor an injunction. This Court has "long acknowledged the importance of the patent system in encouraging innovation." *Sanofi-Synthelabo*, 470 F.3d at 1383. That is especially true in the pharmaceutical context because the incentive to invest "in drug research and development" "would be adversely affected by taking market benefits away from the patentee and giving them to [an] accused infringer." *Celsis*, 664 F.3d at 931-32. Those interests are amplified here because of Novartis's substantial investments in research and development, which have consistently expanded the benefits for patients from ENTRESTO® and in other therapeutic areas. Add1355-1356(¶¶111-114). In contrast, MSN is not known for investing in research and development of new therapies. Add1359(¶120).

The significant harm to Novartis and the public outweighs any harm MSN would suffer. MSN has never argued that it cannot be protected by an adequate bond, which Novartis is willing to post.

IV. THIS COURT SHOULD IMMEDIATELY ENTER AN INJUNCTION PENDING THIS MOTION'S RESOLUTION

This Court should immediately enter an administrative injunction to maintain the status quo while considering this motion. Appellate courts, including this one, have regularly granted temporary relief to "freeze legal proceedings until the court can rule on a party's request for expedited relief" to "buy[] the court time to deliberate" on the motion's merits. *United States v. Texas*, 144 S. Ct. 797, 798 (2024) (Barrett and Kavanaugh, J.J., concurring) (collecting cases); *Marine Polymer Techs. v. HemCon*, 395 F. App'x 701, 702 (Fed. Cir. 2010) (granting administrative stay to preserve status quo).

CONCLUSION

To prevent MSN from launching as soon as July 16, 2025, this Court should enjoin MSN's commercial manufacture, use, offer to sell, or sale within the United States or importation into the United States of its ANDA products, immediately while resolving this motion and then until the appeal is resolved.

Dated: July 14, 2025

Respectfully submitted,

/s/ Jared L. Stringham
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07/13/25

CERTIFICATE OF COMPLIANCE

The foregoing filing complies with the relevant type-volume limitation of the Federal Rules of Appellate Procedure and Federal Circuit Rules because the filing has been prepared using a proportionally spaced typeface and includes 5,192 words, excluding the parts of the brief exempted by the Rules.

Dated: July 14, 2025 /s/ Jared L. Stringham

CERTIFICATE OF SERVICE

I hereby certify that I electronically filed the foregoing with the Clerk of the Court for the United States Court of Appeals for the Federal Circuit by using the CM/ECF system on July 14, 2025.

I certify that on July 14, 2025, I served the confidential version of this brief on counsel for MSN at rjuang@daignaultiyer.com, rdaignault@daignaultiyer.com, kwarner@rmmslegal.com, rakoczy@rmmslegal.com, dmazzochi@rmmslegal.com, and jritthamel@rmmslegal.com.

Dated: July 14, 2025

/s/ Jared L. Stringham
Jared L. Stringham

NOVARTIS PHARMACEUTICALS CORPORATION V. MSN PHARMACEUTICALS, INC.

Case No. 25-1927 (Fed. Cir.)

ADDENDUM TABLE OF CONTENTS

[1] All docket entries are to *In re Entresto (Sacubitril/Valsartan) Patent Litigation*, No. 20-md-2930-RGA (D. Del.), unless noted otherwise.

		Dr. Park's Raman Spectra of Amorphous TVS Versus Physical Mixture of Amorphous Valsartan Disodium and Amorphous Sacubitril Sodium (PTX 1279)	
		Summary Exhibit Pursuant to Fed. R. Evid. 1006, Dr. Matzger's Raman Maps of MSN's 49/51 mg ANDA Product Sample (AJM-XXVIII-2.3) and Overlays of Raman Spectra (PTX 1709)	Add1198
	1930-16	Exhibit 16 to Plaintiff's Brief In Support of Final Judgment, Declaration of Daniel DiMeo in Support of Novartis's Motion for Injunctive Relief Against MSN	Add1210
	1930-17	Exhibit 17 to Plaintiff's Brief In Support of Final Judgment, Declaration of Kristin Miller	Add1237
	1930-18	Exhibit 18 to Plaintiff's Brief In Support of Final Judgment, Declaration of Christopher A. Vellturo, Ph.D. Concerning Irreparable Harm	Add1250
	1930-19	Exhibit 19 to Plaintiff's Brief In Support of Final Judgment, Declaration of DeForest McDuff, Ph.D.	Add1290
	1930-20	Exhibit 20 to Plaintiff's Brief In Support of Final Judgment, Declaration of Bharrat Reddy Chintapally	Add1294
	1931	Declaration of John C. Jarosz Associated with Plaintiff's Proposed Final Judgment Against MSN	Add1302

CONFIDENTIAL MATERIAL OMITTED

The non-confidential version of this addendum redacts material filed under seal pursuant to the protective order issued by the district court. As required by Federal Circuit Rule 25.1(e)(1)(B), the table below notes the specific pages with redacted material in the non-confidential addendum and the general nature of that material.

Description of Redacted Material in Non-Confidential Addendum

Document	Pages	Description
Exhibit 16 to Plaintiff's Brief In Support of Final Judgment, Declaration of Daniel DiMeo in Support of Novartis's Motion for Injunctive Relief Against MSN	Add1211, 1213-1219	Novartis's confidential financial, technical, and sales information
Exhibit 18 to Plaintiff's Brief In Support of Final Judgment, Declaration of Christopher A. Vellturo, Ph.D. Concerning Irreparable Harm	Sealed in its entirety	Novartis's confidential financial, technical, and sales information
Exhibit 19 to Plaintiff's Brief In Support of Final Judgment, Declaration of DeForest McDuff, Ph.D.	Add1291-1293	MSN's confidential financial, technical, and sales information
Exhibit 20 to Plaintiff's Brief In Support of Final Judgment, Declaration of Bharrat Reddy Chintapally	Add1295-1299	Novartis's and MSN's confidential financial, technical, and sales information
Declaration of John C. Jarosz Associated with Plaintiff's Proposed Final Judgment Against MSN	Sealed in its entirety	Novartis's confidential financial and sales information

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

In re Entresto (Sacubitril/Valsartan) Patent Litigation	C.A. No. 20-2930-LPS
NOVARTIS PHARMACEUTICALS CORPORATION, Plaintiff, v. ALKEM LABORATORIES LTD., AUROBINDO PHARMA USA INC., AUROBINDO PHARMA LTD., BIOCON PHARMA LIMITED, BIOCON LIMITED, BIOCON PHARMA, INC., CRYSTAL PHARMACEUTICAL (SUZHOU) CO., LTD., LAURUS LABS LIMITED, LAURUS GENERICS INC., LUPIN ATLANTIS HOLDINGS, S.A., LUPIN LIMITED, LUPIN INC., LUPIN PHARMACEUTICALS, INC., NANJING NORATECH PHARMACEUTICAL CO., LIMITED, TEVA PHARMACEUTICALS USA, INC., TORRENT PHARMA INC., TORRENT PHARMACEUTICALS LTD., Defendants.	C.A. No. 19-1979-LPS

NOVARTIS PHARMACEUTICALS CORPORATION, Plaintiff, v. ALEMBIC PHARMACEUTICALS LIMITED, ALEMBIC PHARMACEUTICALS, INC., MACLEODS PHARMACEUTICALS LTD., MACLEODS PHARMA USA, INC., Defendants.	C.A. No. 19-2021-LPS
NOVARTIS PHARMACEUTICALS CORPORATION, Plaintiff, v. DR. REDDY'S LABORATORIES, INC., DR. REDDY'S LABORATORIES, LTD., HETERO USA INC., HETERO LABS LIMITED, HETERO LABS LIMITED UNIT III, MSN PHARMACEUTICALS INC., MSN LABORATORIES PRIVATE LIMITED, MSN LIFE SCIENCES PRIVATE LIMITED, NOVUGEN PHARMA (MALAYSIA) SDN. BHD., ZYDUS PHARMACEUTICALS (USA) INC., CADILA HEALTHCARE LTD., Defendants.	C.A. No. 19-2053-LPS

NOVARTIS PHARMACEUTICALS CORPORATION, Plaintiff, v. ALEMBIC PHARMACEUTICALS LIMITED, ALEMBIC PHARMACEUTICALS, INC., Defendants.	C.A. No. 20-74-LPS
NOVARTIS PHARMACEUTICALS CORPORATION, Plaintiff, v. LUPIN ATLANTIS HOLDINGS, S.A., LUPIN LIMITED, LUPIN INC., LUPIN PHARMACEUTICALS, INC., Defendants.	C.A. No. 20-415-LPS
NOVARTIS PHARMACEUTICALS CORPORATION, Plaintiff, v. MYLAN PHARMACEUTICALS, INC., Defendant.	C.A. No. 20-445-LPS

[PROPOSED] STIPULATED PROTECTIVE ORDER

WHEREAS discovery in the above-captioned consolidated actions (the "Actions") may involve the disclosure of certain documents, things, and information in the possession, custody, or control of Plaintiff Novartis Pharmaceuticals Corporation and Defendants to these Actions (the "Defendants" or "Defendant Groups"[1]), or nonparties that constitute or contain trade secrets

[1] "Defendant Group" herein shall mean a group of Defendants, each of which comprises a sacubitril/valsartan ANDA-filing entity and its related entities, if any. In these consolidated proceedings, there currently are 17 Defendant Groups:

(1) Alembic Pharmaceuticals Limited and Alembic Pharmaceuticals, Inc. (collectively, "Alembic");

(2) Alkem Laboratories Ltd. ("Alkem");

(3) Aurobindo Pharma USA Inc. and Aurobindo Pharma Ltd. (collectively "Aurobindo");

(4) Biocon Pharma Limited, Biocon Limited, and Biocon Pharma, Inc. (collectively, "Biocon");

(5) Crystal Pharmaceutical (Suzhou) Co., Ltd. ("Crystal Pharma");

(6) Dr. Reddy's Laboratories, Inc. and Dr. Reddy's Laboratories, Ltd. (collectively, "Dr. Reddy's");

(7) Hetero USA Inc., Hetero Labs Limited, and Hetero Labs Limited Unit III (collectively, "Hetero");

(8) Laurus Labs Limited and Laurus Generics Inc. (collectively, "Laurus");

(9) Lupin Atlantis Holdings, S.A., Lupin Limited, Lupin Inc., and Lupin Pharmaceuticals, Inc. (collectively, "Lupin" for both ANDA Nos. 213808 and 213809);

(10) Macleods Pharmaceuticals Ltd. and Macleods Pharma USA, Inc. (collectively, "Macleods");

(11) MSN Pharmaceuticals Inc., MSN Laboratories Private Limited, and MSN Life Sciences Private Limited (collectively, "MSN");

(12) Mylan Pharmaceuticals Inc. ("Mylan");

or other confidential research, development, or proprietary business information within the meaning of Fed. R. Civ. P. 26(c)(1)(G);

WHEREAS such confidential information must be protected to preserve the legitimate business interests of the parties or nonparties;

WHEREAS the parties, through counsel, have stipulated to the entry of this Protective Order for the purpose of advancing the progress of these Actions and to prevent unnecessary dissemination or disclosure of their respective confidential information; and

WHEREAS the parties, through counsel, stipulate that good cause exists for the entry of this Protective Order pursuant to Fed. R. Civ. P. 26(c) to safeguard against improper disclosure or use of confidential information produced in the Actions;

It is hereby ORDERED that the following provisions shall govern the conduct of further proceedings in these Actions:

Definitions

1. The term "Protected Information" shall include all information that the designating party believes constitutes, discloses, or relates to proprietary business information, processes, operations, research, technical or developmental information, production, marketing, sales, shipments, or other proprietary data or information of commercial value not generally available to the public, including, but not limited to, trade secrets. The information contained

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(13) Nanjing Noratech Pharmaceutical Co., Limited ("Noratech");

(14) Novugen Pharma (Malaysia) Sdn. Bhd. ("Novugen");

(15) Teva Pharmaceuticals USA, Inc. ("Teva");

(16) Torrent Pharma Inc. and Torrent Pharmaceuticals Ltd. (collectively, "Torrent"); and

(17) Zydus Pharmaceuticals (USA) Inc. and Cadila Healthcare Ltd. (collectively, "Zydus").

therein and all copies, abstracts, excerpts, analyses, or other writings that contain, reflect, reveal, suggest, or otherwise disclose such Protected Information shall also be deemed Protected Information. Each party shall act in good faith in designating information as Protected Information.

2. "Confidential" or "CONFIDENTIAL" information means Protected Information designated in accordance with paragraph 8.

3. "Highly Confidential" or "HIGHLY CONFIDENTIAL — ATTORNEYS' EYES ONLY" information means Protected Information that is the subset of Confidential information designated in accordance with paragraph 10.

4. "Special Protected Data" or "SPECIAL PROTECTED DATA" means Protected Information designated in accordance with paragraph 12.

5. The term "Qualified Person" shall mean:

a. The Court and any Court personnel involved with these Actions;

b. Outside counsel of record, other attorneys of their firm, their legal assistants, and members of their support staffs (collectively, "Outside Counsel"), subject to the provisions regarding individuals as referenced in paragraphs 6 and 7 below;

c. Any independent expert or consultant who is retained by counsel solely for the purpose of assisting in these Actions, subject to the provisions of paragraph 25 below;

d. Photocopy services;

e. Professional translators who are retained by the attorneys for the parties for the purposes of this litigation;

f. Stenographic reporters, official court reporters, and their assistants who are engaged in such proceedings as are necessary for the preparation and trial of these Actions;

g. Jury or trial consultants and persons employed or retained by them solely in providing litigation support services to the parties' outside counsel law firms;

h. Document imaging and database services and consultants retained to set up, maintain, and/or operate litigation databases for these Actions;

i. Graphics or design consultants retained to prepare demonstrative or other exhibits for use in these Actions;

j. Up to two in-house legal personnel[2] for the receiving party who are responsible for monitoring and/or supervising these Actions subject to the provisions of paragraphs 6 and 7 below.

(i) When Plaintiff is the receiving party, up to two (2) in-house legal personnel employed by Plaintiff, and their respective secretarial, clerical, paralegal and other supporting personnel, shall be covered by this subparagraph 5.j. These in-house legal personnel shall include:

- For Novartis Pharmaceuticals Corporation: Peter J. Waibel.

Plaintiff reserves the right to propose to designate at a later date one additional in-house legal personnel employed by Plaintiff. Before designated in-house legal personnel for Plaintiff may receive Protected

[2] In-house legal personnel designated by Plaintiff shall be an individual who is a U.S. attorney admitted to practice law in one or more courts in this country. In-house legal personnel designated by Defendants shall be an individual who is an attorney or counsel, or, if not an attorney or counsel, personnel in the intellectual property department or legal department/division of a party. For avoidance of doubt, all in-house legal personnel are subject to the provisions of paragraphs 6 and 7. For further avoidance of doubt, designated in-house legal personnel further shall have no competitive decision making authority, as defined by *U.S. Steel v. United States*, 730 F.2d 1465, 1468 n.3 (Fed. Cir. 1984) (*i.e.*, "a counsel's activities, association, and relationship with a client that are such as to involve counsel's advice and participation in any or all of the client's decisions (pricing, product design, etc.) made in light of similar or corresponding information about a competitor").

Information, Plaintiff must serve by email upon counsel of record for all producing parties a completed and signed undertaking in the form of Exhibit A attached hereto from such in-house legal personnel, but a *curriculum vitae* is not required. If Plaintiff seeks to add or replace in-house legal personnel after entry of this Protective Order, it must provide Defendants with the name, title, and job description of the person along with the undertaking attached as Exhibit A, but a *curriculum vitae* is not required. Defendants may object for cause to the proposed disclosure of Protected Information to originally designated, additional, or replacement in-house legal personnel by serving a written objection on every other party within seven (7) days after receiving the copy of the signed declaration. Failure to timely object shall operate as a waiver of the objection. If any Defendants object to the proposed disclosure, their particular Protected Information shall not be disclosed to such person except by order of the Court or by written consent of the objecting party. In the event that a motion is made, the Defendants objecting shall have the burden of proving that disclosure should not be made and Plaintiff shall have the burden of providing sufficient information on all topics described in this paragraph for the Court to reasonably make that determination.

(ii) When Defendants are the receiving party, up to two (2) in-house legal personnel employed by each Defendant Group, and their respective secretarial, clerical, paralegal and other supporting personnel, shall be

covered by this subparagraph 5.j. These in-house legal personnel shall include:

- For Alembic: ____.
- For Alkem: ____.
- For Aurobindo: ____.
- For Biocon: ____.
- For Crystal Pharma: ____.
- For Dr. Reddy's: ____.
- For Hetero: ____.
- For Laurus: ____.
- For Lupin: ____.
- For Macleods: ____.
- For MSN: ____.
- For Mylan: ____.
- For Noratech: ____.
- For Novugen: ____.
- For Teva: ____.
- For Torrent: ____.
- For Zydus: ____.

Defendants reserve the right to propose to designate at a later date additional in-house legal personnel employed by Defendants. Before designated in-house legal personnel for Defendants may receive Protected Information, Defendants must serve by email upon counsel of record for

Plaintiff the name, title, and job description of the person along with a completed and signed undertaking in the form of Exhibit A attached hereto from such in-house legal personnel, but a *curriculum vitae* is not required. If Defendants seek to add or replace in-house legal personnel after entry of this Protective Order, they must provide Plaintiff with the name, title, and job description of the person along with the undertaking attached as Exhibit A, but a *curriculum vitae* is not required. Plaintiff may object for cause to the proposed disclosure of Protected Information to originally designated, additional, or replacement in-house legal personnel by serving a written objection on every other party within seven (7) days after receiving the copy of the signed declaration. Failure to timely object shall operate as a waiver of the objection. If Plaintiff objects to the proposed disclosure, its Protected Information shall not be disclosed to such person except by order of the Court or by written consent of the objecting party. In the event that a motion is made, Plaintiff shall have the burden of proving that disclosure should not be made and the Defendants involved shall have the burden of providing sufficient information on all topics described in this paragraph for the Court to reasonably make that determination.

k. Any other person who is designated as a Qualified Person by order of the Court or by written agreement of the parties.

Restrictions on Individuals with Access to Protected Information

6. The Qualified Persons specified in subparagraphs 5.b., 5.c., and 5.j. who have received access to Protected Information may not engage in prosecution of patent applications claiming formulations, complexes, co-crystals, or other combinations of sacubitril and valsartan, including any methods of manufacture, use, or administration of formulations, complexes, or other combinations in any proportion of sacubitril and valsartan, hydrates of sacubitril and valsartan or water content of sacubitril and valsartan, any polymorphic forms of sacubitril and valsartan or co-crystals of sacubitril and valsartan, for a period beginning when such Qualified Person first accesses Protected Information and ending eighteen (18) months from the end of this Action (including any appeals thereof) without prior approval to do so by agreement of the parties. For the avoidance of doubt, the restrictions set forth in this section shall preclude any Qualified Person that has accessed Protected Information from advising, participating in, providing any input or performing any decision-making in any way in any patent term extension proceedings before the United States Patent and Trademark Office for the patents currently in litigation and any patent asserted at a later time in this litigation. For the further avoidance of doubt, nothing herein shall preclude any Qualified Person from any work relating to asserting infringement of a patent-in-suit for which a patent term extension has been granted. For the further avoidance of doubt, nothing herein shall preclude any Qualified Person from any work relating to any post-grant proceeding before the Patent Trial and Appeal Board under 35 U.S.C. §§ 311 *et seq.* or 35 U.S.C. §§ 321 *et seq.* or pre- or post-grant proceedings before any foreign patent authority; provided, however, that no Qualified Person that has accessed Protected Information shall provide any input, or otherwise participate in any way in the drafting or submission of any amendments to any claims in any reexamination, post-grant review or *inter*

partes review proceeding or pre- or post-grant proceedings before any foreign patent authority (including providing recommendations regarding drafting, crafting, or amending claims to persons engaged on behalf of the receiving party in such activities) relating to formulations, complexes, other combinations in any proportion of sacubitril and valsartan, hydrates of sacubitril and valsartan or water content of sacubitril and valsartan, any polymorphic forms of sacubitril and valsartan or co-crystals of sacubitril and valsartan, including any methods of manufacture, use, or administration of formulations, complexes, other combinations, or co-crystals of sacubitril and valsartan but such Qualified Person may participate in arguing for the validity of amended claims. For the avoidance of doubt, the restrictions in this paragraph shall not apply to a Qualified Person who views Protected Information limited only to the identity of a supplier or manufacturer of a Defendant's active ingredient or drug products from whom discovery may be sought. The restrictions in this paragraph apply only to individuals, and not to the firms or organizations by which they are employed, nor to individuals who have received access to Protected Information solely in their capacity as clerical staff.

7. The Qualified Persons specified in subparagraphs 5.b., c., and j. who have received access to Protected Information shall not be involved in any petitioning, counseling, litigation, or other work before or involving the FDA, or any equivalent foreign regulatory body, concerning formulations, complexes, other combinations, or co-crystals of sacubitril and valsartan, including any methods of manufacture, use, or administration of formulations, complexes, other combinations in any proportion of sacubitril and valsartan, hydrates of sacubitril and valsartan or water content of sacubitril and valsartan, any polymorphic forms of sacubitril and valsartan or co-crystals of sacubitril and valsartan, including but not limited to the preparation or submission of any FDA correspondence (*e.g.*, citizen petitions) regarding approval

requirements for formulations of the above, for a period beginning when such Qualified Person first had access to Protected Information and ending eighteen (18) months from the end of this Action (including any appeals thereof), without prior approval to do so by agreement of the Parties. For the avoidance of doubt, the restrictions set forth in this section shall preclude any Qualified Person that has accessed Protected Information from advising, participating in, providing any input or performing any decision-making in any way in any patent term extension proceedings before the FDA for the patents currently in litigation and any patent asserted at a later time in this litigation. For the further avoidance of doubt, nothing herein shall preclude any Qualified Person from any work relating to asserting infringement of a patent-in-suit for which a patent term extension has been granted. Nothing in this provision prevents the Qualified Person from performing work before the FDA solely for obtaining or maintaining approval of the receiving party's own NDA or ANDA, provided no opposing party's Protected Information is used or disclosed, or from preparing, submitting, or corresponding with the FDA regarding any citizen petition filed with the FDA before any of the above-captioned actions were filed, provided no opposing party's Protected Information is used, or any citizen petition not based on any opposing party's Protected Information. The restrictions in this paragraph apply only to individuals, and not to the firms or organizations by which they are employed, nor to individuals who have received access to Protected Information solely in their capacity as clerical staff.

Use of Protected Information

8. A producing party may designate any material "CONFIDENTIAL" for protection under this Protective Order where that material constitutes or discloses "CONFIDENTIAL" information. "CONFIDENTIAL" information, as that term is used herein, comprises information (regardless of how it is generated, stored or maintained) or tangible things that the

producing party in good faith contends to constitute or contain information that is: (a) confidential, sensitive, competitive, or potentially invasive of an individual's privacy interests; (b) not generally known in the context or form as known by the producing party; (c) not normally revealed to the public or third parties or, if disclosed to third parties, is such that the producing party would require such third parties to maintain the information in confidence; and (d) information (regardless of how generated, stored, or maintained) or tangible things that qualify for protection under standards developed under Fed. R. Civ. P. 26(c). Confidential information may be contained in discovery information or materials produced or obtained in these Actions by or through any means and by or through any person or entity. The Confidential information contained therein and all copies, recordings, abstracts, excerpts, analyses or other writing that contain, reveal, or otherwise disclose such Confidential information shall also be deemed Confidential information. Identification of types of documents in this paragraph shall not be an admission by either party that such documents are relevant or admissible in these Actions.

9. Access to any "CONFIDENTIAL" information shall be limited to Qualified Persons as described in paragraph 5.

10. A producing party may designate any material "HIGHLY CONFIDENTIAL — ATTORNEYS' EYES ONLY" for protection under this Protective Order where the producing party believes in good faith that the material constitutes or discloses highly sensitive business information or items, the unrestricted disclosure of which to a requesting party or a receiving party would create a substantial risk of harm or give a competitive advantage to others which comprises or contains particularly sensitive information of the party and its affiliates, or information received in confidence from third parties, including, but not limited to, the producing

party's planned commercial products and planned licensing agreements. As that term is used herein, "HIGHLY CONFIDENTIAL — ATTORNEYS' EYES ONLY" information and items consist of: (a) highly sensitive information relating to the development of pharmaceutical products; (b) highly sensitive planned licensing and/or settlement agreements; (c) pending patent, trademark, and copyright applications, foreign or domestic, unless published or otherwise publicly available; (d) current or future financial documents (for example P&L statements, business strategy projected future sales, pricing, customer/vendor agreements, revenue, cost or profit information); (e) sensitive marketing plans and forecasts, or financial information related to sacubitril/valsartan products; (f) information tending to reveal the identities of a party's present or prospective customers, or distributors or the personal information of a party's employees; or (g) any other information a producing party believes in good faith could cause irreparable harm to its business if disclosed to personnel for the receiving party. For the avoidance of doubt, technical information relating to the products at issue in these Actions, including investigational new drug applications (INDs), new drug applications (NDAs), abbreviated new drug applications (ANDAs) and related FDA correspondence, Drug Master Files, test data relating to physical and/or chemical properties, and materials concerning research and development shall be designated "HIGHLY CONFIDENTIAL — ATTORNEYS' EYES ONLY". Identification of types of documents in this paragraph shall not constitute an admission by any party that such documents are relevant or admissible in these Actions.

11. Access to "HIGHLY CONFIDENTIAL — ATTORNEYS' EYES ONLY" information and items shall be limited strictly to the persons designated as having access to

"CONFIDENTIAL" information in subparagraphs 5.a.-5.i. and 5.k.,[3] except that, unless otherwise agreed, no outside counsel who is involved in competitive decision-making, as defined by *U.S. Steel v. United States*, 730 F.2d 1465, 1468 n.3 (Fed. Cir. 1984) (*i.e.*, "a counsel's activities, association, and relationship with a client that are such as to involve counsel's advice and participation in any or all of the client's decisions (pricing, product design, etc.) made in light of similar or corresponding information about a competitor"), shall have access to material designated "HIGHLY CONFIDENTIAL — ATTORNEYS' EYES ONLY."

12. A producing party may designate any material "SPECIAL PROTECTED DATA" for protection under this Protective Order where the producing party believes in good faith that the information, including personally identifiable information, is subject to federal, state, or foreign Data Protection Laws or other privacy obligations. Examples of such Data Protection Laws includes, without limitation, The Gramm-Leach-Bliley Act, 15 U.S.C. § 6801 *et seq.* (financial information); The Health Insurance Portability and Accountability Act and the regulations thereunder, 45 C.F.R. Part 160 and Subparts A and E of Part 164 (medical information); Regulation (EU) 2016/679 of the European Parliament and of the Council of 27

[3] Highly Confidential Information may be disclosed to individuals designated pursuant to Paragraph 5.j as set forth in paragraph 45 below. Solely with respect to Plaintiff and Teva, information designated as Highly Confidential information and/or Special Protected Data of Plaintiff or Teva may also be disclosed to Representatives of Teva and Plaintiff designated pursuant to paragraph 5.j., only to the extent Representatives designated pursuant to Paragraph 5.j. are attorneys admitted to practice in the United States and to the extent the Highly Confidential information or Special Protected Data is (a) contained in or attached to documents filed or intended in good faith to be filed with the Court (including drafts thereof); (b) marked in good faith and substantively discussed at a deposition taken in connection with this case; (c) referenced in a response to a discovery request or initial discovery required under Delaware Default Standard for Discovery paragraph 4 or in a draft response to a discovery request or draft initial discovery required under Delaware Default Standard for Discovery paragraph 4 intended in good faith to be served on a party; (d) referenced in an expert report or in a draft expert report intended in good faith to be served on a party; or (e) necessary to make key strategic litigation decisions on issues of infringement.

April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data, and repealing Directive 95/46/EC (General Data Protection Regulation); the German Federal Data Protection Act of June 30, 2017; the Belgian Law of December 8, 1992 on Privacy Protection in relation to the Processing of Personal Data (Belgium personal information); the Federal Data Protection Act of 1992 (Swiss personal information); Personal Information Protection and Electronic Documents Act (PIPEDA), S.C. 2000, c. 5 (Canada personal information); The Federal Law on Protection of Personal Data held by Private Parties (published July 5, 2010) (Mexico personal information); and The Personal Information Protection Act (Law No. 57 of 2003) (Japan personal information); and the U.K. Data Protection Act 2018. "SPECIAL PROTECTED DATA" shall be handled by the receiving party with the highest care and shall be afforded at least the protections of "HIGHLY CONFIDENTIAL — ATTORNEYS' EYES ONLY" information, but may require additional protections depending on the nature of the information, in which case the parties shall meet and confer in good faith, and, if unsuccessful, shall move the Court for appropriate relief.

13. Protected Information that was produced by a party under D. Del. L.R. 26.2 prior to entry of this Protective Order shall be deemed designated "HIGHLY CONFIDENTIAL – ATTORNEYS' EYES ONLY," unless the designation for the Protected Information is specified elsewhere in this Protective Order as "CONFIDENTIAL," in which case the Protected Information shall be deemed designated as "CONFIDENTIAL."

14. Access to "SPECIAL PROTECTED DATA" shall be limited strictly to the persons designated as having access to "HIGHLY CONFIDENTIAL — ATTORNEYS' EYES ONLY" information.

15. Protected Information will be used solely for the purpose of asserting, maintaining, monitoring, supervising, prosecuting, defending, or settling any claim in these Actions, including any appeal and retrial, whether included in an original complaint or counterclaim or amended complaint or counterclaim. Any information that becomes available to any party through the inspection, measuring, analyzing, or testing of any sample or item designated Confidential information or Highly Confidential information pursuant to this Protective Order shall also be considered Confidential information or Highly Confidential information, as the case may be.

16. Nothing in this Protective Order shall prevent any person, including a Qualified Person, from making use of any information that is designated as Protected Information if such information:

a. at the time of disclosure hereunder, was already in the public domain by publication or otherwise;

b. since the time of disclosure hereunder, has become, through no act or failure on the part of the receiving party, part of the public domain by publication;

c. at the time of disclosure hereunder, was already lawfully in the possession of the receiving party and was not acquired directly or indirectly from the producing party or from any nonparty under obligation of confidence to the producing party;

d. after disclosure hereunder, was acquired by the receiving party from a nonparty lawfully possessing the same and having no obligation of confidence to the producing party hereunder;

e. the producing party agrees may be disclosed to a nonparty under no obligation of confidentiality; or

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f. after disclosure hereunder, was developed by the receiving party independently of any Confidential information, Highly Confidential information or Special Protected Data from the producing party.

17. If any person disputes or challenges the designation of any information as Protected Information based on any ground specified in subparagraphs a. – f. of paragraph 16 above, such information shall nevertheless be treated according to its specific designation as Protected Information ("CONFIDENTIAL," "HIGHLY CONFIDENTIAL — ATTORNEYS' EYES ONLY," and/or "SPECIAL PROTECTED DATA") in accordance with the provisions of this Protective Order until such designation is removed by order of the Court or by written consent of the designating party.

Disclosure of Protected Information

18. Protected Information shall not be made available to anyone other than a Qualified Person (or, in the case of "HIGHLY CONFIDENTIAL – ATTORNEYS' EYES ONLY" information or "SPECIAL PROTECTED DATA," the persons identified in paragraph 5 above), or the party who produced such Protected Information, except as otherwise provided in this Protective Order.

19. Protected Information, including all copies, summaries, abstracts, excerpts, indices, and descriptions of such material, shall be held in confidence by the receiving party, shall be used only by a Qualified Person as set forth in this Protective Order, and shall not be used for any purpose other than in connection with these Actions, any appeal therefrom, and remands thereto, including, without limitation, for any research, development, patent prosecution, commercial, marketing, regulatory, FDA citizen petition or other competitive purpose. All Qualified Persons receiving Protected Information are expressly prohibited from

using or disclosing such information in connection with any practice before or communication with the United States Patent and Trademark Office, the United States Food and Drug Administration, the United States Pharmacopoeia, or their counterpart organizations in any foreign jurisdiction. Nothing contained in this Protective Order shall preclude any party from using its own Protected Information in any manner it sees fit, without prior consent of any party or the Court. Nothing contained in this Protective Order shall restrict any party's counsel from rendering advice to its clients with respect to these Actions and, in the course thereof, relying upon Protected Information, provided that in rendering such advice counsel shall not disclose any other party's Protected Information other than in a manner provided for in this Protective Order. Nothing in the foregoing shall prohibit counsel with access to Protected Information from advising their client about overall litigation strategy, including, but not limited to, the potential effects of these Actions on FDA approval.

20. No party may disclose the Protected Information of any Defendant Group to any other Defendant Group without prior written approval of the producing party, which approval shall not be unreasonably withheld. If one party wishes to disclose information from any Defendant Group to any other Defendant Group, the party desiring to make such disclosure and the original producing party shall promptly meet and confer to reach agreement on what information, if any, may be disclosed, before contacting the Court. If the parties are unable to agree, they shall promptly submit their dispute to the Court for resolution using the discovery dispute letter procedures in paragraph 9.o. of the Scheduling Order. A party disclosing Protected Information of any Defendant Group to any other Defendant Group shall provide notice to the receiving Defendant Group that the produced information contains Protected Information of another Defendant Group that is being produced with the consent of the Defendant Group to

which the information belongs. For the avoidance of doubt, each Defendant within a Defendant Group may share its Protected Information, or the Protected Information of another Defendant within that same Defendant Group, with the other members of that same Defendant Group.

21. A document that contains or reveals Protected Information may be shown to any person who authored or previously had access to or knowledge of the document, as demonstrated by the document itself or by foundation testimony during a deposition, hearing, or trial.

22. Protected Information may be disclosed to a witness testifying under oath if the witness is an officer, director, employee, consultant, expert, representative, or designee under Fed. R. Civ. P. 30(b)(6) of the party who produced such Protected Information.

23. This Protective Order shall not prevent counsel from examining a witness testifying under oath in a good-faith effort to determine whether the witness has discoverable information about the Protected Information.

24. Nothing in this Protective Order shall prevent disclosure of Protected Information if the designating party consents to such disclosure or if the Court, after notice to all parties, orders such disclosure.

25. Counsel desiring to disclose a party's Protected Information to an individual according to subparagraphs 5.c. or 5.j. above, or any other person according to subparagraph 5.k. above shall first obtain a signed declaration in the form shown in attached Exhibit A from that person. For independent experts or consultants according to subparagraph 5.c. above, or for any changes to the individuals identified in subparagraph 5.j. above, at least seven (7) days in advance of the proposed disclosure of any Protected Information to that person, counsel shall serve that person's signed declaration by electronic mail on the party or parties who disclosed the Protected Information. The identification of an independent expert or consultant according to

subparagraph 5.c. above shall include the full name and professional address and/or affiliation of the proposed expert or consultant, an up-to-date *curriculum vitae*, including a list of the cases in which the expert or consultant has testified at deposition, at a hearing, or at trial within the last four (4) years. A party may object for cause to the proposed disclosure by serving a written objection on every other party within seven (7) days after receiving the copy of the signed declaration. Failure to timely object shall operate as a waiver of the objection. If a party objects to the proposed disclosure, the objecting party's Protected Information shall not be disclosed to such person except by order of the Court or by written consent of the objecting party, (i) the parties agree to meet and confer in good faith regarding the objection within seven (7) days of the written objection; and (ii) if the parties cannot reach an agreement, the objecting party may file a letter under the Court's discovery dispute procedures in paragraph 9.o. of the Scheduling Order within seven (7) days of the meet and confer. If a motion is made, the objecting party shall have the burden of proving that disclosure should not be made. Outside counsel of record shall retain copies of all signed declarations but need not provide signed declarations to the producing party, except as provided in this paragraph 25.

26. If a party intends to reveal Protected Information of another party during a trial, court appearance, or hearing, which is open to the public, the party intending to reveal such Protected Information shall provide reasonable notice and opportunity to object to the party that produced the Protected Information, unless consent from the party that produced the Protected Information was previously obtained.

Identification and Marking of Protected Information

27. Any party or third party may designate as "Confidential," "Highly Confidential – Attorneys' Eyes Only," or "Special Protected Data" all or any part of any discovery or other

materials produced or served in these Actions, or filed with the Court, including, without limitation, documents and things, pleadings, motions, briefs, contentions, expert reports, interrogatory answers, deposition testimony, and responses to requests for admission, which contain sensitive information protectable under Fed. R. Civ. P. 26(c)(1)(G), as set forth in paragraphs 8, 10, and 12 above.

28. Any document or other tangible thing that contains or reveals Protected Information shall be labeled with the legend "CONFIDENTIAL INFORMATION UNDER PROTECTIVE ORDER," "HIGHLY CONFIDENTIAL INFORMATION UNDER PROTECTIVE ORDER — ATTORNEYS' EYES ONLY," and/or "SPECIAL PROTECTED DATA," or a marking of like import. Such marking shall appear on each page of the document that contains Protected Information. For pleadings, briefs, discovery responses, declarations, and expert reports, such marking need only appear on the first page of the document. Any document or other tangible thing so labeled and the information that it contains or reveals shall be treated in accordance with the provisions of this Protective Order. If a pleading, brief, discovery response, declaration, or expert report is marked as containing Protected Information as permitted above, the receiving party of such document may request the serving party to identify which party's Protected Information is contained in the pleading, brief, discovery response, declaration, or expert report and to identify by highlighting what specific information is considered Protected Information. The serving party shall respond to such request within three (3) business days, unless the receiving party must take action within five (5) business days or less, in which case the serving party shall respond to such request within one (1) business day. Any Protected Information not reduced to documentary or physical form or which cannot be conveniently

labeled shall be so designated by a party by serving a written notification on the receiving party within a reasonable amount of time after disclosure.

29. When a party initially produces documents for inspection, no marking need be made by the producing party in advance of the inspection. For purposes of the inspection, all documents shall be treated as containing Protected Information. After the receiving party selects specified documents for copying, the producing party shall appropriately mark the copies of the selected documents before they are provided to the receiving party.

30. If a party believes that inspection, measuring, testing, sampling, or photographing of that party's processes, products, equipment, premises, or other property pursuant to Fed. R. Civ. P. 34 will reveal or disclose information that is in good faith deemed Confidential information, Highly Confidential information or Special Protected Data, that party shall advise in advance the party or parties seeking such discovery that the inspection, measuring, testing, sampling, or photographing will be permitted on a "Confidential," "Highly Confidential," or "Special Protected Data" basis as appropriate and that the material discovered and any information derived from that material, shall be treated according to the appropriate designation. Nothing contained in this Protective Order shall be deemed a waiver of any requirements for showing of good cause under the Court rules or of any right of the producing party to seek an order from the Court regarding further conditions for any inspection of its premises.

31. Only Qualified Persons, the deponent, and the court reporter and videographer shall be allowed to attend any portion of a deposition in which Protected Information is used or elicited from the deponent. The deposition of any witness (or any portion of such deposition) that encompasses "HIGHLY CONFIDENTIAL — ATTORNEYS' EYES ONLY" information

or "SPECIAL PROTECTED DATA" shall be taken only in the presence of persons who are qualified to have access to such information.

32. Unless otherwise agreed, deposition transcripts shall be treated as containing "CONFIDENTIAL INFORMATION UNDER PROTECTIVE ORDER" during the thirty (30) day period following receipt of the transcript, unless the transcript was previously designated as containing "HIGHLY CONFIDENTIAL — ATTORNEYS' EYES ONLY" information or "SPECIAL PROTECTED DATA," in which case the transcript will be treated in accordance with such designation. If a party contends that the deposition transcript contains "HIGHLY CONFIDENTIAL — ATTORNEYS' EYES ONLY" information, "SPECIAL PROTECTED DATA," or "CONFIDENTIAL" information, that party will be required to affirmatively designate, in writing or on the record, the transcript, or portions of the transcript, as "HIGHLY CONFIDENTIAL — ATTORNEYS' EYES ONLY," "SPECIAL PROTECTED DATA," or "CONFIDENTIAL" information within the thirty (30) day period following receipt of the transcript. If they do not, the transcript shall be treated as not containing Protected Information.

33. A non-party to the litigation, *e.g.*, a third party producing information pursuant to subpoena, may designate such information as Protected Information as set forth in paragraph 27 above. If so designated, such Protected Information shall be subject to the same restrictions and conditions as information designated by any party as Protected Information. Nothing in this provision shall limit the ability of a party to designate such information produced by a non-party as Protected Information.

34. If, in responding to a discovery request, subpoena, other legal process or otherwise in these Actions, a non-party discloses Protected Information belonging to or owned by a party, the information disclosed by the non-party shall be accorded the same protection as if

it were received from a producing party under this Protective Order. In such event, a party, in good faith believing the information disclosed to be its Protected Information, may designate such information pursuant to this Protective Order.

35. If discovery in these Actions requests the production by a party of information, the disclosure of which would breach an express or implied agreement with a non-party to maintain such information in confidence, the party requested to produce the information shall first give written notice to the non-party with a copy of this Protective Order. When such written notice is given to the non-party, the party requested to produce the information will advise the requesting party that such notice has been given. If the non-party consents to production, the requested information shall be produced in accordance with this Protective Order. If the non-party objects to production, the party requested to produce it shall not produce the information without an order from the Court directing it to do so. Any such non-party shall have standing to appear in these Actions to file motions and oppose motions, as necessary, to protect such non-party's rights in such information.

Inadvertent Production of Incorrectly or Undesignated Material

36. Any producing party may change a designation to Confidential, Highly Confidential, or Special Protected Data (or withdraw a designation) regarding any material that it has produced by notifying counsel for each receiving party in writing. A producing party's inadvertent production of documents or materials without designating such documents or materials as Protected Information or incorrectly designating the level of confidentiality of such documents or materials shall not be deemed a waiver in whole or in part of a claim of confidentiality as to such documents or materials. Upon notice to the receiving party of such inadvertent production of undesignated or incorrectly designated documents or materials, the receiving party shall cooperate to restore the confidentiality or appropriate level of

confidentiality of the inadvertently undesignated or incorrectly designated information, including (i) not making any further disclosure or communication to such newly designated material except as provided for in this Protective Order; (ii) within four (4) business days of the discovery of such notice, take reasonable steps to notify any persons known to have possession of any material with the original designation (or lack of designation) and alert those persons of the effect of such a designation or change in designation under this Protective Order; (iii) for material newly designated as Highly Confidential or Special Protected Data, promptly retrieve or have destroyed all copies and transcription of such originally designated (or undesignated) material from any persons known to have possession of such material who are not proper Qualified Persons under paragraphs 5 and 18; and (iv) for material newly designated as Confidential, promptly retrieve or have destroyed all copies and transcriptions of such originally designated (or undesignated) material from any persons known to have possession of such material who are not proper Qualified Persons under paragraph 5. Properly marked documents, reflecting the new designation, shall be promptly provided by the producing party. No showing of error, inadvertence, or excusable neglect shall be required for re-designation.

Storage of Protected Information

37. The recipient of any Confidential information, Highly Confidential information, or Special Protected Data provided under this Protective Order shall maintain such information in a reasonably secure and safe manner that ensures that access is limited to the persons authorized under this Protective Order, and shall further exercise the same standard of due and proper care with respect to the storage, custody, use, and/or dissemination of such information as is exercised by the recipient with respect to its own proprietary information.

Data Security

38. Any person in possession of Confidential information, Highly Confidential information, or Special Protected Data shall maintain an information security program that includes reasonable administrative, technical, and physical safeguards designed to protect the security and confidentiality of such Confidential information, Highly Confidential information, or Special Protected Data, to protect against any reasonably anticipated threats or hazards to the security of such Confidential information, Highly Confidential information, or Special Protected Data, and to protect against unauthorized access to Confidential information, Highly Confidential information, or Special Protected Data. To the extent a party or person does not have an information security program, they may comply with this provision by having the Confidential information, Highly Confidential information, or Special Protected Data managed by and/or stored with electronic discovery vendors or claims administrators that maintain such an information security program. If a receiving party or authorized recipient discovers any loss of Confidential information, Highly Confidential information, or Special Protected Data or a breach of security, including any actual or suspected unauthorized access, relating to another party's Confidential information, Highly Confidential information, or Special Protected Data, the receiving party or authorized recipient shall: (a) promptly provide written notice to the disclosing party of such breach; (b) investigate and make reasonable efforts to remediate the effects of the breach, and provide disclosing party with assurances reasonably satisfactory to the disclosing party that such breach shall not recur; and (c) provide sufficient information about the breach that the disclosing party can reasonably ascertain the size and scope of the breach. The receiving party or authorized recipient agrees to cooperate with the producing party or law enforcement in investigating any such security incident. In any event, the receiving party or authorized recipient

shall promptly take all necessary and appropriate corrective action to terminate the unauthorized access.

Personally Identifiable Information

39. Personally identifiable information that a party has designated as Special Protected Data as defined above in paragraph 12, based on its good-faith belief that the information is subject to federal, state, or foreign Data Protection Laws, data privacy laws, or other privacy obligations, or any of the information contained therein, shall be handled by counsel for the receiving party with the highest care.

Inadvertent Production of Privileged or Protected Documents

40. Pursuant to Federal Rule of Evidence 502(d), the production of documents or materials that the producing party thereafter claims to be subject to the attorney-client privilege, work-product immunity, or other protection mandated by local law shall not constitute a waiver of such privilege, immunity, or other protection in these Actions or any other action. After receiving written notice from the producing party that documents or materials subject to the attorney-client privilege, work-product immunity, or other protection have been produced, the receiving party shall not copy or otherwise disseminate the documents or materials, nor shall it disclose their substance. Any further review of such documents or materials shall be limited to purposes under subparagraphs 40.a. – 40.c., unless otherwise ordered by the Court or agreed to by the parties. In addition, the receiving party shall return the documents or materials and all copies within five (5) business days from receiving notice, or provide written confirmation of the destruction of the original and all copies of the identified documents, including all documents and things generated by a receiving party which documents and things contain information derived from the returned/destroyed materials. The receiving party shall not utilize the information contained in the returned/destroyed documents or materials for any purpose, or

disseminate or transmit such information, except in connection with a motion to compel under subpart c. of this section.

a. If the receiving party wishes to contest that any such document or thing is protected by the attorney-client privilege, work-product immunity, or other protection mandated by local law, the receiving party shall so notify the producing party in writing when the document or thing is returned to the producing party ("Notice of Designation"). If the receiving party provides a Notice of Designation, the receiving party may retain one (1) copy of the document(s) for use only in connection with the filing of a motion to compel production of the document(s). If the receiving party does not file a motion to compel within the timeframe set out herein, the document(s) must be returned or destroyed by the deadline for filing a motion to compel. If the receiving party files a motion to compel and its motion is denied, the receiving party must return or destroy the document within five (5) business days after entry of the Court order denying the motion to compel.

b. Within five (5) business days after receiving a Notice of Designation, the producing party shall provide to the receiving party for each such document or thing a description of the basis for the claim of privilege, immunity, or other protection.

c. Within five (5) business days after receiving such description, the receiving party may seek relief from the Court to compel production of such documents and things, the protection of which is still disputed. In any such motion to compel production of the returned/destroyed document, the receiving party shall not rely upon in any manner or assert as a ground for ordering production the fact or circumstances of the production. Any such motion shall be filed under seal.

d. The parties may stipulate to extend the time periods set forth in subparagraphs 40.b. and 40.c. above.

e. Nothing in this order overrides any attorney's ethical responsibilities to refrain from examining or disclosing materials that the attorney knows or reasonably should know to be privileged and to inform the disclosing party that such materials have been produced.

f. The disclosing party retains the burden—upon challenge pursuant to subparagraph 40.c. above—of establishing the privileged or protected nature of the information in question.

g. Nothing in this order limits the right of any party to petition the Court for an *in camera* review.

h. This Protective Order does not preclude a party from voluntarily waiving the attorney-client privilege or work product protection. The provisions of Federal Rule of Evidence 502(a) apply when the disclosing party uses or indicates that it may use information produced under this order to support a claim or defense.

i. Under this Protective Order, the provisions of Federal Rule of Evidence 502(b)(2) are inapplicable.

j. Nothing in this Protective Order shall be construed to require the production of Protected Information deemed by counsel possessing such information to be privileged or otherwise protected from discovery.

<u>Challenges to Protected Information Designation</u>

41. A party shall not be obligated to challenge the propriety of a Protected Information designation at the time made, and a failure to do so shall not preclude a subsequent challenge thereto. If a party disagrees at any time with a Protected Information designation made by another party, the parties shall make a good-faith attempt to resolve the dispute on an

informal basis. If the parties cannot resolve the dispute, the objecting party may seek appropriate relief from the Court, and the designating party shall have the burden of proving that its Protected Information designation is proper.

Filing of Protected Information

42. If a party deems it necessary to submit its or another party's Protected Information to the Court, the party shall file or designate the Protected Information under seal in accordance with D. Del. LR 5.1.3, and nothing in this Protective Order shall preclude the producing party from requesting that the Court seal the Protected Information. The sealing of the Protected Information shall remain in effect until further order of the Court. A second copy of any pleading or paper specifically intended for review by the Court may be hand-delivered to the Court's chambers appropriately marked, in order to assure that the same is brought promptly to the Court's attention.

43. The Clerk of the Court is directed to maintain under seal any pleading, motion, brief, memorandum, exhibit, affidavit, declaration, transcript, response to a discovery request, or other paper filed with the Court that has been designated, in whole or in part, as containing or revealing Protected Information.

44. Nothing in this Protective Order shall prevent a party from using any document, material or other information that is designated as Protected Information under this Protective Order at a hearing, trial or other court proceeding in these Actions, provided such use is otherwise consistent with the terms of this Protective Order, and such document, material or other information shall not lose its confidential status through such use. The parties shall take all steps permitted by the Court and reasonably required to protect the confidentiality of such designated information during such use.

45. To the extent Protected Information of another party relating to Plaintiff's Entresto product or the products that are the subject of each Defendant Group's ANDAs, including INDs, NDAs, ANDAs and related FDA correspondence, Drug Master Files, test data relating to physical and/or chemical properties, and materials concerning research and development is designated as Highly Confidential Information, such Protected Information may also be disclosed to individuals designated pursuant to paragraph 5.j.,[4] only to the extent the Highly Confidential Information is (a) substantively referenced or relied upon in documents filed or intended in good faith to be filed with the Court (including drafts thereof); (b) marked in good faith and substantively discussed at a deposition taken in connection with this case; (c) referenced in a response to a discovery request or initial discovery required under Delaware Default Standard for Discovery paragraph 4 or in a draft response to a discovery request or draft initial discovery required under Delaware Default Standard for Discovery paragraph 4 intended in good faith to be served on a party; (d) referenced in an expert report or in a draft expert report intended in good faith to be served on a party; or (e) necessary to make key strategic litigation decisions on issues of infringement. For purposes of clarity, nothing in this paragraph shall allow disclosure of Protected Information designated as Highly Confidential of one Defendant Group to individuals designated pursuant to paragraph 5.j. of any other Defendant Group, except as provided in paragraph 20.

46. Any Special Protected Data, including personal health information, that is protected under state, federal or foreign Data Protection Laws or other privacy obligations and is disclosed in discovery by a party or third party to these Actions shall not be used or disclosed in

[4] Novartis may designate only two attorneys who must be admitted to practice in the United States.

open court unless in accordance with the further order of the Court, such as an order of the Court sealing the courtroom. The Court will enter further orders as necessary to control the conduct of hearings and trial as it relates to the use of Confidential or Highly Confidential information. Absent an agreement between the parties otherwise, the designating party shall bear the burden of seeking relief from the Court to prevent the designating party's Special Protected Data from being revealed during a trial, court appearance, or hearing that is open to the public.

47. Upon the failure of the filing or lodging party to properly designate information and file under seal, any party or third party who in good faith believes that designation and filing under seal is required may move the Court to file said information under seal within ten (10) business days of learning of the defective filing or lodging. Notice of such designation shall be given by the moving party to all parties in these Actions. Nothing in this provision relieves a party of liability of damages caused by failure to properly file Protected Information under seal. The burden of proving that such information should be sealed shall at all times remain on the party which designated the information as Protected Information.

48. If a party intends to reveal Protected Information of another party during a trial, court appearance, or hearing which is open to the public, the party intending to reveal such Protected Information shall provide reasonable notice and opportunity to object, unless consent from the designating party is previously obtained. Absent an agreement between the parties otherwise, the designating party shall bear the burden of seeking relief from the Court to prevent the designating party's Protected Information from being revealed during a trial, court appearance, or hearing that is open to the public.

49. Notwithstanding the above, each party reserves the right to request at a hearing or trial that the courtroom be closed to the public and any non-qualified party representatives during

the introduction of testimony or argument regarding or exhibits containing Protected Information.

Discoverability of Expert Materials

50. Without limiting the applicability of Fed. R. Civ. P. 26(a)(2) and (b)(4), at least the following categories of data, information, or documents need not be disclosed by any Party or Person, and are outside the scope of permissible Discovery Materials under this Protective Order and Fed. R. Civ. P. 26(a)(2) and (b)(4): Draft reports or disclosures, expert notes, written or oral communications and notes of communications between any expert and counsel for a party, including any attachments.

Third-Party Requests

51. If any third party requests the production of any Protected Information, including, but not limited to, a request by subpoena, the receiving party in possession of such Protected Information must:

a. Notify the producing party within 7 days of receiving the request; and

b. Take all lawful steps necessary to assert (or permit the producing party to assert) all applicable protections, including but not limited to:

(i) Permitting the producing party a reasonable opportunity to intervene and be heard, and

(ii) Defending the asserted rights, privileges, and immunities if the producing party cannot be heard.

Other Proceedings

52. By entering this Protective Order and limiting the disclosure of information in this case, the Court does not intend to preclude another court from finding that information may be relevant and subject to disclosure in another case. Any person or party subject to this order who

becomes subject to a motion to disclose another party's information designated as Protected Information pursuant to this Protective Order shall promptly notify that party of the motion so that the party may have an opportunity to appear and be heard on whether that information should be disclosed.

<u>Miscellaneous</u>

53. No party shall be responsible to another party for any use made of information that was produced and not designated as Protected Information.

54. Should any Protected Information be disclosed, through inadvertence or otherwise, by a receiving party to any person not duly authorized to receive such information under this Protective Order, then the receiving party responsible for such disclosure shall promptly notify counsel for the party that disclosed the information of all pertinent facts and make every effort to prevent further unauthorized disclosure, including retrieving all copies of the Protected Information from the unauthorized recipient(s) thereof and requesting that each such recipient execute the declaration attached as Exhibit A.

55. Nothing herein shall prevent the parties from redacting personally identifying information or other information protected under Swiss, German, or U.K. privacy law, the General Data Protection Regulation, or other foreign laws and regulations. The parties recognize that certain witnesses may be subject to laws concerning data privacy, data secrecy or cross-border data transfer restrictions that require protections or limitations beyond those described herein. The parties shall work in good faith to address such issues as they arise and to abide by relevant foreign laws and regulations.

56. When the inadvertent or mistaken disclosure of any information contained in any document that the producing party believes is non-responsive is discovered by the producing party and is brought to the attention of the receiving party, the producing party shall promptly

produce a properly redacted replacement version of said document to the receiving party. Upon receipt of the redacted replacement version, the receiving party shall immediately return and/or destroy all copies of the original version of said document, and confirm in writing to the producing party that it has done so.

57. The parties acknowledge that the production of documents and ESI located abroad, in particular in Europe and Switzerland, will need to comply with local laws, including laws concerning cross-border data transfer, data privacy and data secrecy protections. Further, the parties acknowledge that there are restrictions on the taking of depositions outside of the United States. Should any such depositions be needed, the parties will meet and confer to try to resolve any issues that might arise.

58. Nothing in this Protective Order shall prejudice the right of any party to oppose production of any information for lack of relevance, privilege, or any ground other than confidentiality.

59. Nothing in this Protective Order shall prejudice the right of any party to seek at any time a further order modifying this Protective Order.

60. Nothing in this Protective Order shall prejudice the right of any party to bring before the Court at any time the question of whether any greater or lesser restrictions should be placed upon the disclosure of any Protected Information.

61. This Protective Order shall be binding upon the parties hereto, upon their attorneys, and upon the parties' and their attorneys' successors, executors, personal representatives, administrators, heirs, legal representatives, assigns, subsidiaries, divisions, officers, directors, employees, agents, and independent contractors, and other persons or organizations over which they have control. If a person or party withdraws or is dismissed from

these Actions, that person or party's access to Protected Information shall end, and all copies of those materials in the person or party's possession, custody, or control shall be returned or destroyed promptly following withdrawal or dismissal, except as provided in paragraph 64 below.

62. In the event that a new party is added, substituted, or brought in, this Protective Order will be binding on and inure to the benefit of the new party, along with the corresponding obligations on the new party to maintain the confidentiality of the Protected Information, subject to the right of the new party to seek relief from or modification of this Protective Order.

63. To the extent not already addressed above, non-parties who produce information in these Actions may avail themselves of the provisions of this Protective Order.

64. At the conclusion of these Actions, including any appeals, the originals of all produced documents or things designated as Protected Information, and all photocopies thereof (including those provided to outside experts and other third parties), but excluding those provided to the Court, shall, within sixty (60) days of a written request, (a) be returned to the producing party or (b) be destroyed with a representation of such destruction being made to the producing party, except that neither the parties nor the Court shall be obliged to return or destroy any production documents or production things (or any photocopies thereof) that were admitted into evidence at trial or any hearing; incorporated (as an exhibit, appendix, or otherwise) as part of a document filed with or submitted to the Court; or incorporated (as an exhibit, appendix, or otherwise) as part of an expert report. Notwithstanding the foregoing, and subject to a continuing obligation to protect all such material pursuant to this Protective Order, outside counsel and in-house legal personnel identified in subparagraph 5.j. above may retain archive copies of filings, court papers, correspondence, deposition and trial transcripts, deposition and

trial exhibits, expert reports, written discovery responses, and attorney work product (regardless of whether such materials contain or reference information designated as Protected Information).

65. If any party breaches, or threatens to commit a breach, of any of the provisions of this Protective Order, each non-breaching party or third party that produced information subject to this Protective Order shall have the right to ask the Court for any remedies available under law or in equity, including having this Protective Order specifically enforced (without posting any bond) and/or entering a restraining order or injunction (preliminary or permanent) against the breaching party for breaches, threatened or actual. It is agreed and acknowledged that, in the event of any such breach or threatened breach, the breaching party is not entitled to a presumption that money damages or legal remedies are sufficient or adequate to remedy such a breach.

66. The provisions of this Protective Order shall survive and remain in full force and effect after the termination of these Actions (including any appeals). This Court shall retain jurisdiction even after termination of this litigation to enforce this Protective Order and make such amendments, modifications, deletions, and additions to this Protective Order as the Court may from time to time deem appropriate.

67. This Order may be amended as need may arise by written agreement of the parties, subject to Court approval.

68. Each person or entity who receives any Protected Information agrees to subject himself/herself to the jurisdiction of this Court for the purpose of any proceedings relating to the performance under, compliance with, or violation of this Protective Order.

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Dated: August 31, 2020

SO ORDERED this ____ day of ____________________, 2020.

____
THE HONORABLE LEONARD P. STARK
CHIEF UNITED STATES DISTRICT JUDGE

ME1 34154678v.1

EXHIBIT A

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

In re Entresto (Sacubitril/Valsartan) Patent Litigation	)	C.A. No. 20-2930-LPS

AGREEMENT TO BE BOUND

I, _____, having been asked by counsel for Plaintiff / Defendants [circle one] in one or more of the Actions (as defined in the Stipulated Protective Order) to review certain confidential documents or other information that is subjected to the Stipulated Protective Order that has been or will be entered by the District Court for the District of Delaware in the Actions, declare and state under penalty of perjury that:

1. My address is _____.

2. My present employer is _____.

and the address of my present employer is _____.

_____.

3. My present occupation or job description is _____.

4. I have received a copy of the Stipulated Protective Order in these Actions.

5. I have carefully read and understand all of the provisions of the Stipulated Protective Order.

6. I will comply with all of the provisions of the Stipulated Protective Order.

7. I will hold in confidence, will not disclose to anyone not qualified under the Stipulated Protective Order, and will use only for purposes of these Actions, any Protected Information that is supplied to me.

8. At the termination of these Actions, or any time requested by counsel for the party by whom I am employed, I will delete or return each document and each other tangible thing that discloses or reveals any Protected Information to the attorney who provided such document or

other tangible thing to me. Moreover, I will delete or deliver any copies, abstracts, summaries, notes, or other records regarding the contents of any Protected Information to the attorney who provided such Protected Information to me.

9. I understand that, if I violate the provisions of the Stipulated Protective Order, I will be in violation of a Court order and subject to sanctions or other remedies that may be imposed by the Court and potentially liable in a civil action for damages.

10. I hereby submit to the jurisdiction of the United States District Court for the District of Delaware for the purpose of enforcement of the Stipulated Protective Order.

I declare under penalty of perjury of the laws of the United States that the foregoing is true and correct.

Dated: _____ _____

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

In re Entresto (Sacubitril/Valsartan) Patent Litigation	Civil Action No. 20-md-2930-RGA
NOVARTIS PHARMACEUTICALS CORPORATION, Plaintiff, v. MSN PHARMACEUTICALS INC., MSN LABORATORIES PRIVATE LIMITED, MSN LIFE SCIENCES PRIVATE LIMITED, Defendants.	Civil Action No. 22-cv-1395-RGA

TRIAL OPINION

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ANDREWS, U.S. DISTRICT JUDGE:

This case is part of the multi-district litigation of patent infringement claims regarding Plaintiff Novartis Pharmaceuticals Corporation's Entresto. Novartis brought C.A. No. 22-1395 against MSN Pharmaceuticals Inc., MSN Laboratories Private Limited, and MSN Life Sciences Private Limited (together, "MSN"), alleging infringement of its U.S. Patent No. 11,096,918 (the "'918 patent"). (Docket No. 22-1395, D.I. 1 ¶ 1). Novartis accuses MSN of infringing claim 1 of the '918 patent, which MSN disputes. (D.I. 1705 at 1; D.I. 1757 at 1).[1]

I held a four-day bench trial from December 10, 2024 to December 13, 2024. (D.I. 1701, 1702, 1703, 1704, hereinafter cited "Tr.__"). I have reviewed the parties' post-trial briefing. (D.I. 1705, 1757, 1764). Having considered the evidence and testimony, I make the following findings of fact and conclusions of law pursuant to Federal Rule of Civil Procedure 52(a). I find that Novartis has not proved that MSN infringes the '918 patent.

I. BACKGROUND

Novartis is the holder of New Drug Application ("NDA") No. 207620 for Entresto, a tablet with active ingredients sacubitril and valsartan, used to treat heart failure. (Docket No. 22-1395, D.I. 1 ¶ 113). The '918 patent is not listed in the FDA Orange Book for Entresto. (*See* D.I. 1185 at 2). The priority date of the '918 patent is April 4, 2006. ('918 patent). The '918 patent is directed to the chemical compound that comprises Entresto, which is the amorphous solid form of sacubitril, valsartan, and sodium cations ("amorphous TVS"). (*Id.* at Abstract).

MSN submitted an Abbreviated New Drug Application ("ANDA") for approval to market generic versions of Entresto. (Docket No. 22-1395, D.I. 1 ¶ 31). Novartis then initiated this lawsuit.

[1] Unless otherwise specified, the docket referred to is C.A. No. 20-md-2930.

II. LEGAL STANDARD

A patent is directly infringed when a person "without authority makes, uses, offers to sell, or sells any patented invention, within the United States or imports into the United States any patented invention during the term of the patent." 35 U.S.C. § 271(a). Determining infringement is a two-step analysis. *Markman v. Westview Instruments, Inc.*, 52 F.3d 967, 976 (Fed. Cir. 1995) (en banc), *aff'd*, 517 U.S. 370 (1996). First, the court must construe the asserted claims to ascertain their meaning and scope. *Id.* The trier of fact must then compare the properly construed claims with the accused infringing product. *Id.* This second step is a question of fact. *Bai v. L & L Wings, Inc.*, 160 F.3d 1350, 1353 (Fed. Cir. 1998). The patent owner bears the burden of proving infringement by a preponderance of the evidence. *SmithKline Diagnostics, Inc. v. Helena Lab'ys Corp.*, 859 F.2d 878, 889 (Fed. Cir. 1988).

In a Hatch-Waxman case, the plaintiff's infringement claim is based on the accused infringer's future conduct, rather than past acts of infringement. Under § 271(e)(2), the "infringement inquiry . . . is focused on the product that is likely to be sold following FDA approval." *Abbott Lab'ys v. TorPharm, Inc.*, 300 F.3d 1367, 1373 (Fed. Cir. 2002). "Because drug manufacturers are bound by strict statutory provisions to sell only those products that comport with the ANDA's description of the drug, an ANDA specification defining a proposed generic drug in a manner that directly addresses the issue of infringement will control the infringement inquiry." *Id.*

III. ANALYSIS

The '918 patent is directed to amorphous TVS. ('918 patent at Abstract). The only claim at issue is Claim 1 of the '918 patent, which recites:

1. An amorphous solid form of a compound comprising anionic [valsartan[2]], anionic [sacubitril[3]], and sodium cations in a 1:1:3 molar ratio.

(*Id.* at 32:42–46).

I issued a claim construction opinion on May 31, 2024, where I construed "[a]n amorphous solid form of a compound" as "a solid form of a compound in which the amorphous form of the compound predominates. An amorphous solid form is mutually exclusive from a crystalline solid form, but not necessarily mutually exclusive from a partially crystalline solid form."[4] (D.I. 1374 at 5).

The only issue is whether Novartis successfully proved MSN's ANDA infringes claim 1 of the '918 patent by a preponderance of the evidence. MSN withdrew its invalidity arguments at trial. (Tr. 1035:17–19).

A. Findings of Fact

1. Level of Ordinary Skill in the Art

The parties agree on the definition of a person having ordinary skill in the art ("POSA"). A POSA for claim 1 of the '918 patent "is a person with a Ph.D. in chemistry or related field and two or more years of experience with solid forms of pharmaceutical compounds, such as

[2] The chemical name "(S)-N-valeryl-N-{[2'-(1H-tetrazole-5-yl)-biphenyl-4-yl]-methyl}-valine" recited in claim 1 describes valsartan.

[3] The chemical name "(2R,4S)-5-biphenyl-4-yl-4-(3-carboxy-propionylamino)-2-methyl-pentanoic acid ethyl ester" recited in claim 1 describes sacubitril.

[4] The Federal Circuit called this construction into question in an appeal of my denial of Novartis' motion for a preliminary injunction. *Novartis Pharms. Corp. v. MSN Pharms., Inc.*, 2024 WL 4969281, at *5 (Fed. Cir. Dec. 4, 2024). Even if I had adopted a different construction (like Novartis' proposal that no construction was needed, and thus any amount of amorphous TVS could infringe), I would still find that Novartis failed to prove MSN infringes. Novartis failed to prove MSN's ANDA contains any amorphous TVS due to the unreliability of Dr. Park's Raman spectrum.

synthesizing, crystallizing, and characterizing solid forms of pharmaceutical compounds." (Tr. 375:1–6).

2. Raman Spectroscopy

The parties generally agree about how Raman spectroscopy works. Raman spectroscopy provides a way to classify and identify molecular compounds and materials. (*See* Tr. 385:24–386:5). A Raman instrument shines a laser beam into a sample and records the energy levels produced by the sample. (Tr. 385:11–17, 718:8–15). The sample will "scatter" some of the light shined into it. (Tr. 718:8–24). The energy levels measured by the Raman instrument are the differences between the energy of the light shone into the material and the energy of the scattered light. (*Id.*; Tr. 720:10–12). The energy differentials will depend on the vibration of the bonds in the molecules, which will depend on the types of bonds in the molecules. (Tr. 385:11–17, 718:19–24, 720:18–22).

Conducting a Raman spectroscopy test on a sample will produce a Raman spectrum. (*See* Tr. 718:6–24, 720:10–12). A Raman spectrum is a graph with "Raman Shift" (in units of cm^{-1}) on the x-axis and "Intensity" or "Counts" on the y-axis, and it has peaks reflecting the recorded energy levels. (*See, e.g.*, PTX-1709; DTX-780 at 1). The peaks vary in intensity. (*See* Tr. 722:20–22).

A certain molecule, compound, or complex will produce a unique Raman spectrum. (Tr. 385:24–386:5, 719:19–24). The Raman spectrum can be thought of as a "fingerprint." (*Id.*). A Raman spectrum for a sample of a compound should be the same as a Raman spectrum for a different sample of the same compound. (*See id.*).

The Raman spectrum of a physical mixture of multiple compounds will be different from the Raman spectrum of an amorphous complex of the same multiple compounds. (*See* Tr. 730:20–24; '918 patent at 28:64–67).

An unknown compound can be identified by creating a Raman spectrum of the unknown compound and comparing it to reference Raman spectra of known compounds. (*See* Tr. 498:1–3, 829:16–18). If the spectrum of the unknown compound and the spectrum of a known compound generally contain the same peaks and intensity of peaks, one can conclude the unknown compound is the same as the known compound. (*See id.*).

3. Physical Mixtures and Amorphous Complexes

A physical mixture is the combination of two or more compounds with no significant chemical interactions among the compounds. (Tr. 376:9–11). An amorphous complex is the combination of two or more compounds with chemical interactions among the compounds, like "covalent-noncovalent" bonds. (Tr. 376:12–16).

Novartis' expert witness, Dr. Park, created a spectrum of an amorphous physical mixture by making amorphous valsartan disodium and amorphous sacubitril sodium, creating spectra of the two, normalizing the two spectra, then adding the two spectra together. (Tr. 383:11–15, 387:17–19).

MSN argues that the mathematically-created amorphous physical mixture spectrum is unreliable. (D.I. 1757 at 7 n.2). I disagree. Dr. Park testified that adding together the spectra of two components in a physical mixture is an accepted way to create the spectrum of that physical mixture, citing literature to support her testimony. (Tr. 387:24–388:10; JTX-138; JTX-127;

JTX-130). MSN's expert, Dr. McCreery,[5] said, "I don't like that practice, and I would far rather have a real physical mixture." (Tr. 723:14–15). But Dr. McCreery admitted that adding together two spectra to create a physical mixture spectrum is a method used by those in the field and described in relevant literature. (Tr. 723:7–8). Dr. McCreery described the potential distortion in intensity that may result from adding two spectra together (Tr. 722:20–24), but Dr. Park testified extensively that she normalized the spectra before adding them together, and cited literature to support her normalization procedures. (Tr. 425:19–429:23). Dr. McCreery did not say that Dr. Park's methods were inappropriate. He said he did not like it. I think Dr. Park's mathematically-created amorphous physical mixture spectrum is reliable.

4. Dr. Park's Glassy Solid

The parties dispute whether MSN's ANDA is predominately amorphous TVS. Dr. Park created a reference sample (also called the "glassy solid") of purportedly amorphous TVS to compare with MSN's ANDA. The parties dispute whether that reference sample and the corresponding Raman spectrum of the sample are sufficiently reliable.[6]

Amorphous TVS is different from an amorphous physical mixture of valsartan and sacubitril; this the parties agree on. (D.I. 1705 at 1; D.I. 1757 at 1). The parties disagree about

[5] Novartis alleges that Dr. McCreery is not a POSA. (D.I. 1705 at 11). MSN makes no responsive arguments in its post-trial brief. This issue was the subject of a pre-trial *Daubert* motion. (*See* D.I. 1625 at 6 n.6). While true that "testimony on any issue that is analyzed through the lens of an ordinary skilled artisan" must come from an expert qualified as a POSA, *Kyocera Senco Indus. Tools Inc. v. ITC*, 22 F.4th 1369, 1377–78 (Fed. Cir. 2022), the opinions from Dr. McCreery that I rely on are not POSA opinions. I rely on his opinions about Raman spectroscopy. Dr. McCreery is an expert in Raman spectroscopy. (*See* Tr. 716:14–717:21).

[6] Though the parties argue about whether Novartis' reference spectrum is sufficiently "reliable," and I ultimately find the spectrum is not "reliable," the crux of the dispute is credibility of expert testimony. "[D]isputes over the expert's credibility or over the accuracy of the underlying facts" are questions of fact. *Summit 6, LLC v. Samsung Elecs. Co.*, 802 F.3d 1283, 1299 (Fed. Cir. 2015).

whether Dr. Park successfully made amorphous TVS, as opposed to an amorphous physical mixture. The parties point to the Raman spectrum of Dr. Park's glassy solid. Novartis says it is different from the Raman spectrum of an amorphous physical mixture of sacubitril and valsartan; MSN says it is not.

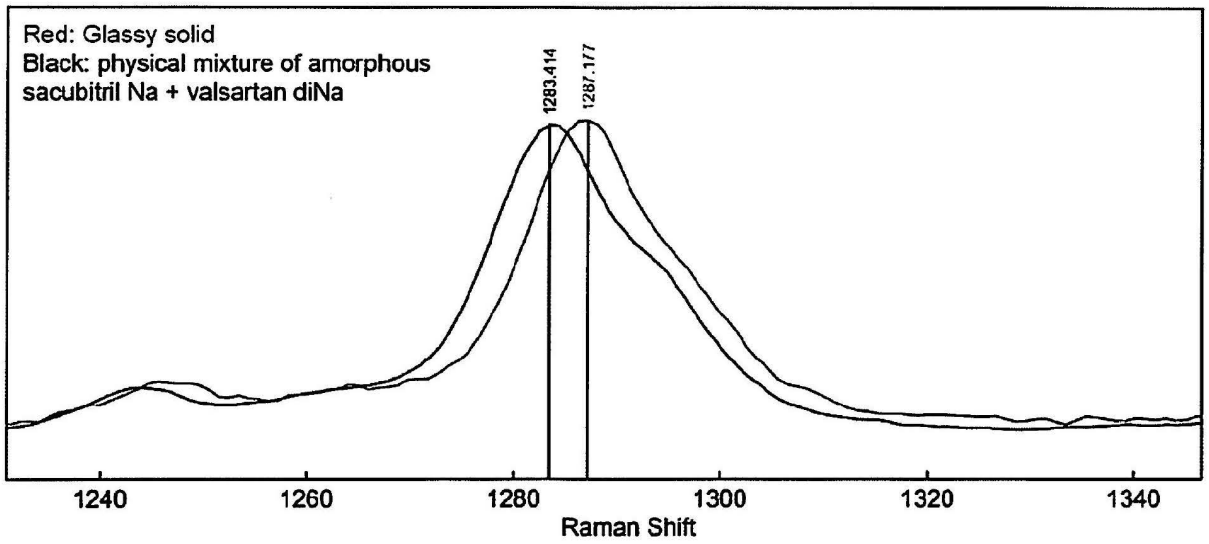
I think the Raman spectrum of Dr. Park's glassy solid is not reliable. That is, I do not think Novartis has shown by a preponderance of the evidence that the reference Raman spectrum is of amorphous TVS.

Dr. Park is the chief operating officer at Triclinic Labs. (Tr. 371:14–15). Dr. Park testified that she created, with assistance from those that work at Triclinic, amorphous TVS according to Example 1 of the '918 patent. (Tr. 373:12–19).[7] Dr. Park then ran tests on her sample to confirm that what she created was, in fact, amorphous TVS. (Tr. 386:13–18). Dr. Park created spectra of her sample from three spectroscopy methods: solid-state nuclear magnetic resonance ("ssNMR"), infrared ("IR"), and Raman. (*Id.*). To confirm that what she made was amorphous TVS, she compared the spectra of her sample to her spectra of an amorphous physical mixture and noted the differences between the two sets of spectra. (Tr. 387:1–11, 388:21–396:18).

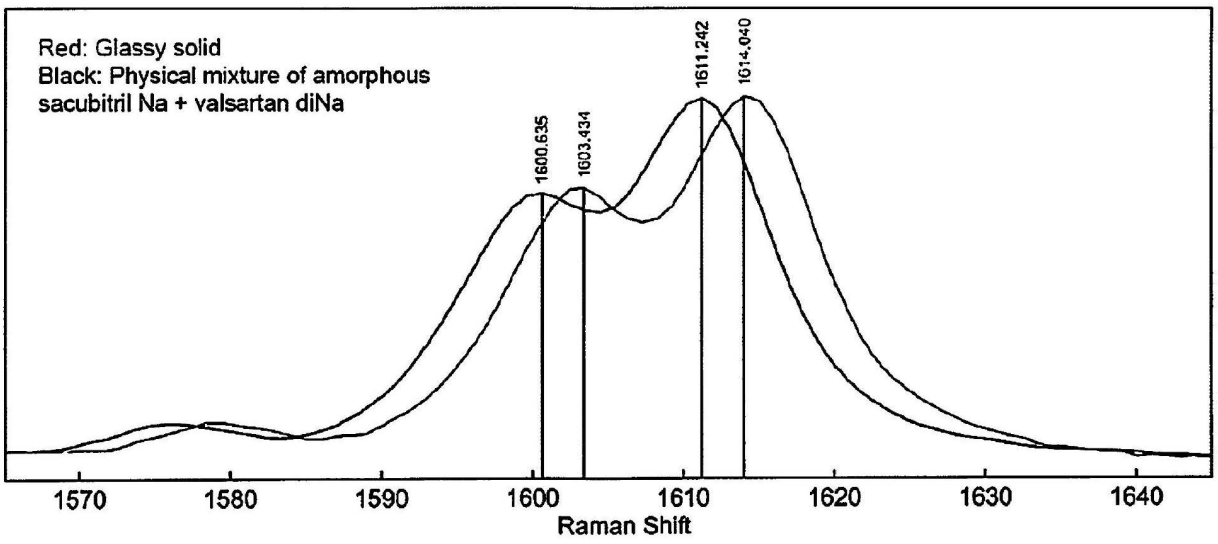
[7] MSN attempts to poke holes in how the glassy solid was made, chiefly arguing that the Triclinic technicians performed more steps than those listed in Example 1 of the '918 patent. (*See* D.I. 1757 at 17). Dr. Park was cross-examined on the issue (*see* Tr. 445:6–448:11), but MSN offered no expert of its own to testify that those extra steps so contaminated the process that the final product could not be amorphous TVS. MSN gives no explanation on how any extra steps affected the process. Though I do find the reference spectrum to be unreliable, I have no reason to doubt Dr. Park's testimony that Triclinic followed Example 1 as faithfully as possible. (*See* Tr. 379:15–17, 445:6–13).

MSN argues that Dr. Park created an amorphous physical mixture, not amorphous TVS, pointing to the similarities between Dr. Park's glassy solid Raman spectrum and her mathematically calculated amorphous physical mixture Raman spectrum. (D.I. 1757 at 7–8).

The reference glassy solid Raman spectrum, purportedly showing a spectrum of amorphous TVS, is strikingly similar to the amorphous physical mixture spectrum. Below are two "zoomed in" portions of the overlaid spectra, as presented by Novartis:



(PTX-1277 at 1 of 2).

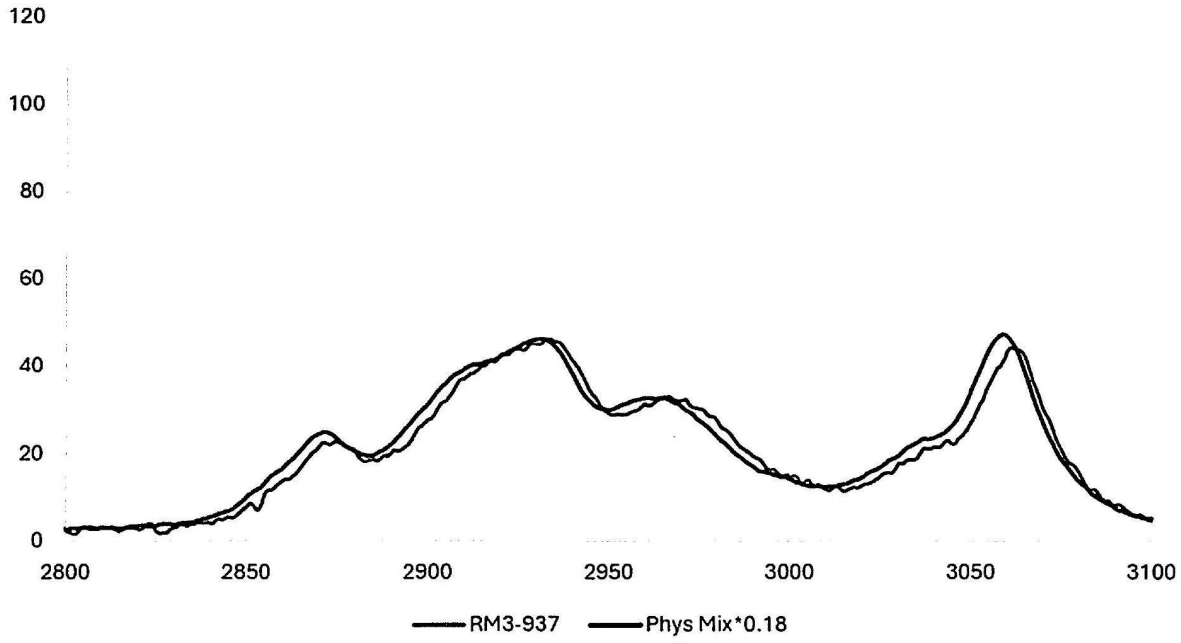


(*Id.* at 2 of 2).

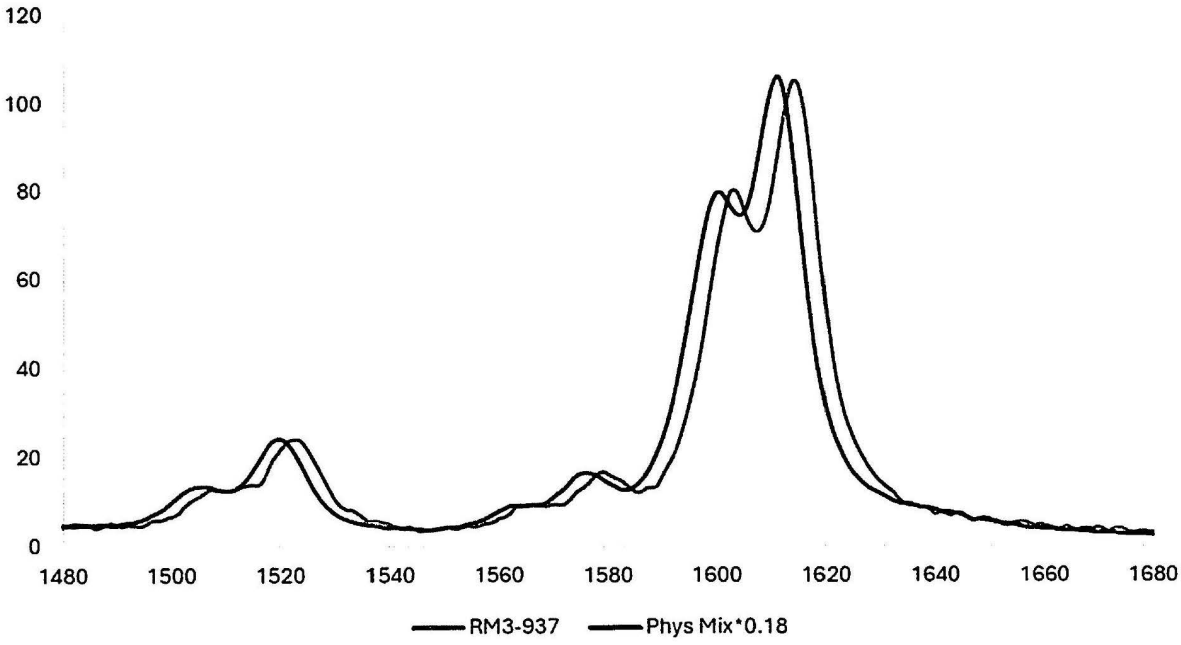
The peaks are at approximately the same height,[8] but the peaks are slightly shifted. That is, the spectrum for Dr. Park's glassy solid is shifted to the right of the amorphous physical mixture spectrum. Novartis points to three peak shifts (which can be seen in the images above) to show that the two spectra are different and that Dr. Park's glassy solid is amorphous TVS. The peak shifts are as follows (listed physical mixture first, Dr. Park's glassy solid second): 1283.4 cm^{-1} to 1287.2 cm^{-1} (difference of 3.8 cm^{-1}), 1600.6 cm^{-1} to 1603.4 cm^{-1} (difference of 2.8 cm^{-1}), and 1611.2 cm^{-1} to 1614.0 cm^{-1} (difference of 2.8 cm^{-1}).[9] (Tr. 394:21–395:5).

But, as testified to by Dr. McCreery, when looking at the Raman spectra as a whole, not just the two zoomed in portions, it appears that the entire Raman spectrum of the glassy solid is shifted approximately 3 cm^{-1} to the right of the Raman spectrum of the physical mixture. (Tr. 725:7–726:15). Below are MSN's depictions of several other regions of the two spectra:[10]

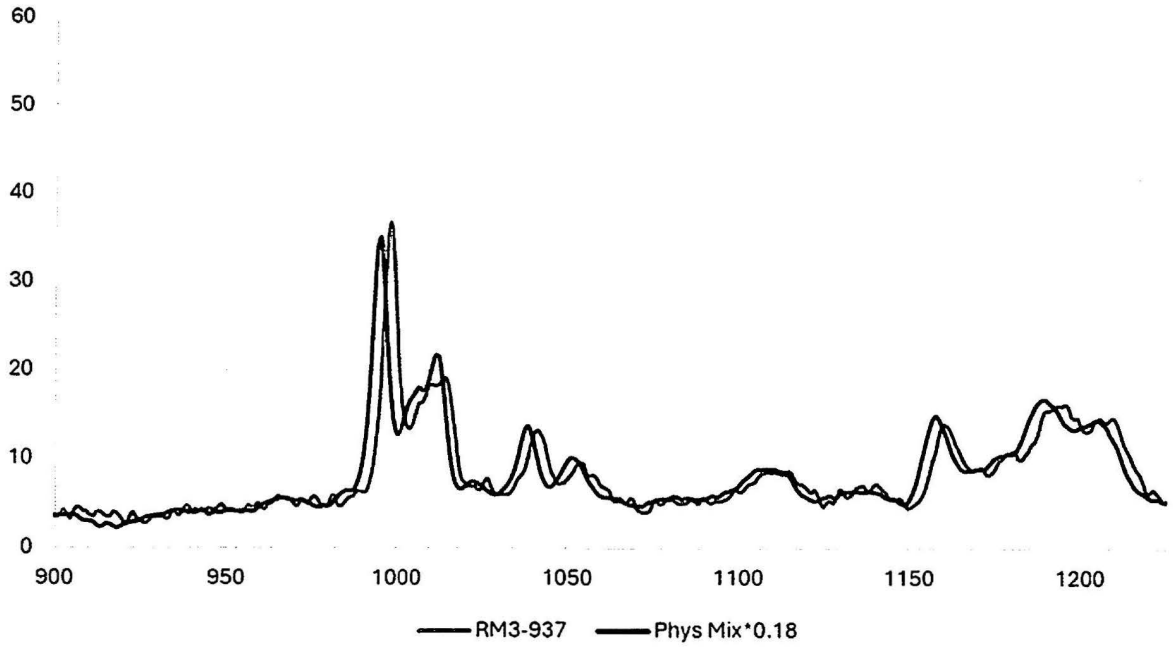
[8] The parties do not address the similarity in peak heights. This is merely my observation.
[9] When asked why the shifts all end in .8 or .7, Dr. Park responded, "[M]y Raman data was collected at about almost one wavenumbers, close to one. So that's why the difference [always ends in] about .8 or .7 because it's close to about 0.9 wavenumber . . . . That's the number of data points." (Tr. 409:18–22). MSN does not raise any issues about this testimony.
[10] MSN did provide a graph with the entirety of the two spectra overlaid, but with Dr. Park's glassy solid spectrum shifted 3 cm^{-1} to show that the spectra are substantially the same. (*See* DTX-646A at 3 of 11). It is nearly impossible to distinguish the two spectra. Perhaps that was MSN's intention, but I think several additional "zoomed in" areas on the spectra, without MSN's 3 cm^{-1} shift, are more informative.



(DTX-646A at 4 of 11).



(*Id.* at 5 of 11).



(*Id.* at 6 of 11).

Novartis argues the peak shifts show that the glassy solid is amorphous TVS, not an amorphous physical mixture, pointing to Redenti, a paper published in 1996. (D.I. 1705 at 3; D.I. 1764 at 7; Tr. 395:7–11). Indeed, Redenti says and shows that, at least with respect to the compounds at issue there, an amorphous complex and an amorphous physical mixture of the components in that complex will display different Raman peaks. (*See* JTX-121 at 3, 5 of 6). But Redenti points to more than just peak shifts. It describes the broadening and weakening of various peaks and bands as other notable differences observed between an amorphous complex and an amorphous physical mixture. (*Id.* at 3 of 6). Redenti does point to peak shifts, too, but no systematic shift of an entire Raman spectrum. (*See id.*). The visual comparing the two Raman spectra in Redenti is shown below:

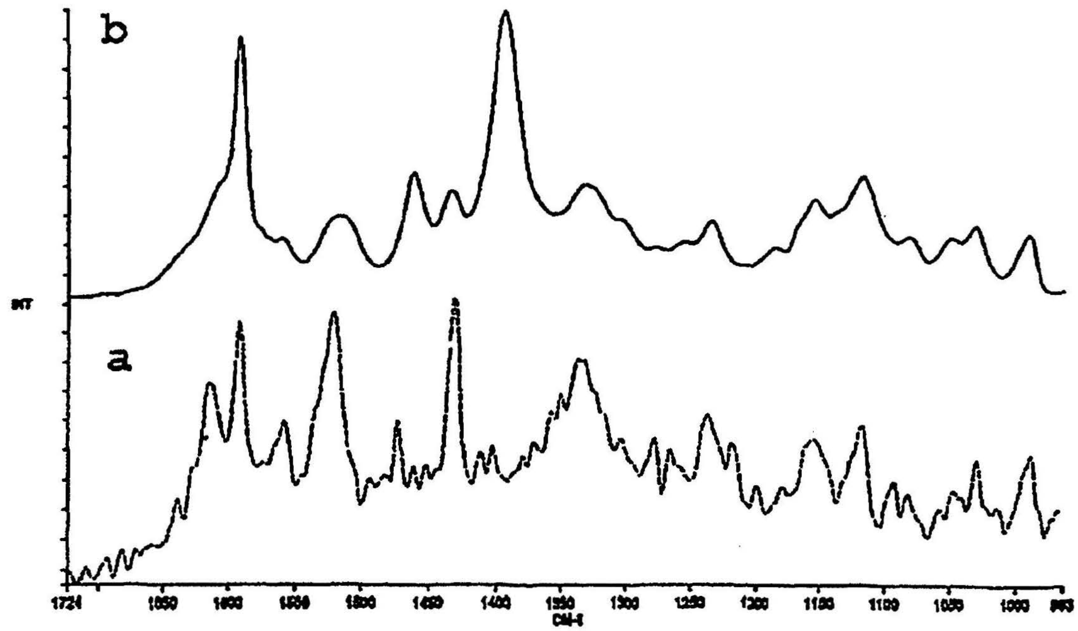


Fig. 3. Diagnostic region of NIR FT-Raman spectra of: (a) physical mixture of the two amorphous components and (b) freeze-dried P:β-CD (laser power: 30 mW/mm^2).

(*Id.* at 5 of 6). Dr. McCreery testified that the changes in peak intensity and shift of some, but not all, peaks show a difference between the two samples in Redenti. (Tr. 730:11–731:17). Redenti itself supports this. (*See* JTX-121 at 3 of 6).

Dr. McCreery testified that the type of systematic shift observed between the amorphous physical mixture Raman spectrum and Dr. Park's glassy solid Raman spectrum is simply "impossible." (Tr. 727:5). He testified that, in considering the bonds and molecular interactions present in an amorphous complex that are not present in an amorphous physical mixture, "most of the molecules shouldn't be affected," and there thus should be no systematic shift between the two spectra. (Tr. 727:5–11). Dr. McCreery testified that, though one spectrum of a sample is typically all that is needed to classify that sample, he would have run several tests and generated several Raman spectra of Dr. Park's glassy solid so he could statistically analyze the spectra and determine if the small changes are indeed significant. (Tr. 736:21–737:6). Dr. McCreery's testimony, combined with Novartis' own reference tending to support his testimony, convince

me that Novartis failed to show by a preponderance of the evidence that MSN's ANDA infringes based on the reference spectrum of Dr. Park's glassy solid.

Novartis has five main arguments in response.

First, Novartis points out that the glassy solid Raman spectrum is not uniformly shifted by precisely 3 cm^{-1}. (D.I. 1705 at 13). That is true. The peak shifts, as calculated by Novartis, are between 1.8 cm^{-1} and 5.7 cm^{-1}. (Tr. 409:7–11). Dr. McCreery testified that a calculated peak shift will depend on how the peak is selected. (Tr. 734:24–735:2). Dr. McCreery testified that most peak-picking software will pick the maximum height of a peak, which is not always the true normalized center of the peak. (*Id.*). He testified that small differences in peaks, like the ones at issue here, need rigorous evaluation to ensure accuracy. (Tr. 735:6–15). Dr. McCreery further testified that most of the peaks selected by Dr. Park were within Dr. Park's margin of error (1 cm^{-1}) of 3 cm^{-1}, and that the largest peak difference (5.7 cm^{-1}) was on a broad band where the peak could have plausibly been selected differently (as shown by Dr. McCreery shifting the glassy solid Raman spectrum 3 cm^{-1} and showing how closely the two spectra line up, including at the purported 5.7 cm^{-1} shift). (Tr. 733:20–737:6). Dr. Park testified that she accurately selected peak points. (Tr. 411:6–413:2). Dr. Park did not testify about how she picked her peaks or what software she used to pick her peaks. (*See* Tr. 411:24–413:2). While true that Dr. McCreery did not perform an analysis showing a peak selection where all peaks are uniformly shifted by 3 cm^{-1}, his testimony sows doubt about Novartis' reference Raman spectrum.

Second, Novartis argues that Dr. Park's instrument was properly calibrated when she conducted Raman spectroscopy on her glassy solid, and MSN has provided no explanation for what would cause a systematic shift in the spectrum other than actual differences between

amorphous TVS and an amorphous physical mixture of sacubitril and valsartan. (D.I. 1705 at 13).

Dr. Park testified that the Raman instrument she used is routinely calibrated using polystyrene, in accordance with American Society of Testing and Materials ("ASTM") standards. (Tr. 414:2–7). That is, the Raman instrument scans polystyrene and produces a spectrum, three peaks in that spectrum are compared to three known polystyrene peaks, and the instrument is calibrated accordingly. (Tr. 414:2–14). Dr. Park's Raman instrument was calibrated three times around the time of her testing her glassy solid: April 13, 2023, June 7, 2023, and August 3, 2023. (Tr. 415:5–7). She tested the glassy solid on April 28, 2023. (Tr. 373:4–8). Dr. Park testified that her "Raman instrument was accurate within plus/minus one wavenumber during [her] testing" and that there were no systematic shifts in the calibration data. (Tr. 414:25–415:2; Tr. 415:15–19). For example, on one calibration day, one peak was off by +1 cm^{-1}, another peak was off by +0.2 cm^{-1}, and another was off by 0.0 cm^{-1}. (Tr. 415:8–14). Dr. Park opined that any difference in peaks among two samples greater than one wavenumber is thus a "real difference between the two samples." (Tr. 415:20–25).

Dr. McCreery led the development of the ASTM standards followed by Dr. Park in calibrating her Raman instrument. (Tr. 737:14–16). He opined that Dr. Park did not do enough to ensure the accuracy of her Raman instrument. (Tr. 738:9–13). Dr. McCreery testified that, after seeing the striking similarities and small differences between the physical mixture and the glassy solid Raman spectra, he would have conducted further testing to ensure that the two spectra were in fact different. (*Id.*). Dr. McCreery did not pinpoint a systemic error that caused the 3 cm^{-1} shift; "It could have various sources." (Tr. 752:20–24).

Though Dr. McCreery and MSN do not point out a specific error in Dr. Park's Raman instrument that caused a uniform shift of 3 cm^{-1}, I do not think that is necessary for MSN to sow doubt about Novartis' reference Raman spectrum. For the reasons explained above, I think the reference Raman spectrum is unreliable. I do not doubt the accuracy of the calibration tests conducted on Dr. Park's Raman instrument. But I credit Dr. McCreery's testimony that such abnormally close and uniformly shifted spectra warrant further testing to confirm that the two spectra are in fact different. This is supported by Novartis' reference, Redenti, that shows that differences in peak positions and intensities among Raman spectra can be used to differentiate between an amorphous complex and a physical mixture, but is silent on a systematic shift with virtually no change in intensity. (*See* JTX-121 at 3, 5 of 6).

Third, Novartis points to other spectroscopy tests that purportedly show Dr. Park's Raman spectrum is of amorphous TVS, not an amorphous physical mixture. (D.I. 1705 at 3). Novartis points to ssNMR and IR spectra. (*Id.*). MSN addressed those spectra in a footnote and offered no expert testimony at trial to counter Dr. Park's testimony that the ssNMR and IR spectra show her glassy solid is amorphous TVS. (D.I. 1757 at 5 n.1; Tr. 743:3–17). MSN's arguments about the purported unreliability of the ssNMR and IR spectra are forfeited. *See Higgins v. Bayada Home Health Care Inc.*, 62 F.4th 755, 763 (3d Cir. 2023). I thus credit Dr. Park's testimony that the ssNMR and IR spectra tend to show that her glassy solid is amorphous TVS. Regardless, I think the Raman spectrum of Dr. Park's glassy solid is unreliable, for the reasons I explain above. Novartis used Dr. Park's Raman spectrum to show MSN's ANDA infringes, not the ssNMR or IR spectra. It is the Raman spectrum, not the glassy solid sample or the ssNMR and IR spectra, that I think is unreliable.

Fourth, Novartis offered testimony from Dr. Park to counter Dr. McCreery's testimony that the systematic shift was "impossible." (D.I. 1705 at 16). Dr. Park testified that it was not impossible for amorphous TVS to generate over twenty Raman peak shifts, pointing to the complexity of amorphous TVS. (Tr. 436:18–437:4). But Dr. Park did not address the crux of Dr. McCreery's testimony: that it was impossible for the entire amorphous Raman spectrum to shift by approximately the same amount. I do not think Dr. Park's testimony helps establish the reliability of her glassy solid Raman spectrum.

Fifth, Novartis argues multiple spectra are not needed to classify a compound, contrary to Dr. McCreery's opinion. (D.I. 1705 at 14–15). Dr. Park testified that a pharmaceutical compound can be classified with one spectrum, citing several pieces of literature for support. (Tr. 422:20–423:20). I do not doubt this. But I credit Dr. McCreery's testimony that when two spectra of two supposedly different materials are "very similar" (Tr. 728:6), multiple spectra would be beneficial so one could run statistical tests to determine if those small differences are significant enough to conclude the two materials are in fact different. (Tr. 736:21–737:6). I note that the sources cited by Dr. Park contain more obvious differences in the Raman spectra (like the emergence of new peaks and changes in intensity). (*See* JTX-121 at 5 of 6; PTX-1225 at 4 of 5; PTX-1228 at 4 of 5; PTX-1223 at 2 of 4).

To further support its position, MSN points to a spectrum from Novartis that MSN alleges is of amorphous TVS, but which is different from Dr. Park's glassy solid spectrum. (D.I. 1757 at 15–16).

Novartis had previously developed "LCZ-696," an amorphous compound; it had spectra of that compound. (*See* Tr. 430:9–11; JTX-104 at 8 of 33). MSN argues amorphous LCZ-696 is amorphous TVS, pointing to deposition testimony of a Novartis employee, Dr. Motto, who was

in charge of the Pharmaceutical and Analytical Development group working on Entresto. (D.I. 1757 at 15–16; *see* Tr. 692:13–25, 693:22–694:2). When asked if Novartis had ever characterized a material as amorphous TVS, Dr. Motto said, "Novartis was able to determine that material they had was amorphous [TVS] based on analytical testing of the next step product [(crystalline LCZ-696)] and physical evaluation of the material that they isolated [(LCZ-696 amorphous to glassy solid)]." (Tr. 695:11–22). Dr. Motto's testimony could be clearer. I understand him to say that Novartis determined amorphous TVS was in fact amorphous by comparing crystalline LCZ-696 to amorphous LCZ-696. Dr. Motto later testified that the glassy solid of Example 1 "was characterized as amorphous LCZ-696 or amorphous [TVS]," seeming to equate the two. (Tr. 697:2–5). Though Dr. Motto does not say so explicitly, it seems quite likely that he equated LCZ-696 with amorphous TVS.

Novartis had an internal presentation discussing, among other things, amorphous LCZ-696. (JTX-104). The presentation has a graph displaying Raman spectra of several materials, including amorphous LCZ-696. (*Id.* at 8 of 33). The amorphous LCZ-696 Raman spectrum is different from Dr. Park's glassy solid Raman spectrum. (Tr. 741:8–16). Peak intensities are different and some peaks are present in one and not in the other. (*Id.*). According to Dr. McCreery, "[S]pectroscopy would never claim those were the same material." (Tr. 741:14–15). Dr. Park agreed that the two spectra were different. (Tr. 462:7–10).

The author of the presentation, Charles Pan, is not an inventor of the '918 patent, and the presentation is dated April 21, 2009 while the '918 patent's priority date is April 4, 2006. (Tr. 430:22–431:10; *see* JTX-104 at 1 of 33; '918 patent). The Raman spectrum for amorphous LCZ-696 in the presentation was produced on February 6, 2007. (Tr. 431:17–19). The presentation

does not say amorphous LCZ-696 is amorphous TVS. (Tr. 431:23–25). None of these things foreclose the possibility that LCZ-696 is amorphous TVS.

Novartis argues that the LCZ-696 in its presentation is not Dr. Park's glassy solid. (D.I. 1764 at 4–5). True. That does not matter. Raman spectroscopy is like a fingerprint; the spectrum of one sample of a compound should be the same as the spectrum of a different sample of the same compound. (*See* Tr. 385:24–386:5, 719:19–24). If amorphous LCZ-696 and Dr. Park's glassy solid are both amorphous TVS, the two spectra should be substantially the same. I note that Novartis offered no testimony saying amorphous LCZ-696 is not amorphous TVS. Novartis merely argues Dr. Motto did not explicitly say the two were the same. (D.I. 1764 at 5).

Based on the timing and Dr. Motto's testimony, I think there is a reasonable likelihood that amorphous LCZ-696 is amorphous TVS. Since the amorphous LCZ-696 spectrum is quite different from Dr. Park's glassy solid spectrum, it too causes me to doubt that Dr. Park's glassy solid Raman spectrum is reliable to use as a reference to compare with MSN's ANDA.

B. Conclusions of Law

1. Adverse Inference

The parties dispute the applicability of an adverse inference. Before trial, I heard a discovery dispute between Novartis and MSN's co-defendants, Gerbera Therapeutics, Inc. and Nanjing Noratech Pharmaceutical Co., Limited (together, "Noratech"). (*See* D.I. 1634 at 3). Noratech went to trial with MSN, but settled its case after trial, and I entered a consent judgment and injunction against Noratech on June 17, 2025. (D.I. 1902). At the discovery dispute, Noratech asserted that Novartis failed to produce Dr. Park's glassy solid sample in violation of Federal Rule of Civil Procedure 26. (*See* D.I. 1634 at 3). At the pretrial conference, I indicated I would take an adverse inference against Novartis for failing to produce the sample. (D.I. 1667 at

31:21–32:4). Novartis re-argues the applicability of an adverse inference, and it argues that any adverse inference does not apply to MSN because MSN was not the defendant that requested the glassy solid. (D.I. 1705 at 34–35).

Whether to impose sanctions, and which sanctions to impose, for discovery violations is in the discretion of the trial court. FED. R. CIV. P. 37(c); *see Grider v. Keystone Health Plan Cent., Inc.*, 580 F.3d 119, 134 (3d Cir. 2009). Novartis gives three reasons for why an adverse inference is not warranted. As I explained at the pretrial conference, I think an adverse inference is warranted, but I address Novartis' arguments. (D.I. 1667 at 31:21–32:4).

First, Novartis argues a sanction for a discovery violation requires prejudice. (D.I. 1705 at 34). I think there is prejudice here. MSN wanted to test the sample Novartis used to show MSN's ANDA infringes but could not. Indeed, counsel for Novartis asked Dr. Park if "Defendants' experts test[ed] the glassy solid of Example 1." (Tr. 397:7–9). Counsel may have been asking if Defendants' experts tested any glassy solid, not just Dr. Park's, but again, Defendants wanted to test Dr. Park's sample in particular.

Second, Novartis argues there must be bad faith for sanctions to be warranted, citing *Robocast v. Microsoft Corp.*, 2014 WL 789086, at *2 (D. Del. Feb. 25, 2014). *Robocast* dealt with spoliation and a party failing to issue a litigation hold to preserve evidence. *Id.* at *1. The case cited in *Robocast*, a Third Circuit case, dealt with spoliation and the sanction of dismissal with prejudice. *Bull v. United Parcel Serv., Inc.*, 665 F.3d 68, 72 (3d Cir. 2012). *Bull* says, "Withholding requires intent," and that sanctions are appropriate only for withheld evidence, not evidence accidentally misplaced. *Id.* at 79. Novartis does not contend the glassy solid was misplaced; indeed, Dr. Park still had it at the time of trial. (Tr. 448:25–449:3). The glassy solid fell under the scope of requested production. Novartis agrees. (D.I. 1667 at 15:5–6). Novartis

argued only that Nanjing Noratech brought up the issue too late. (*Id.* at 14:3–6). There is evidence that Novartis knew the sample existed, knew the sample fell within the scope of requested discovery, and did not provide it. I think that is sufficient to show that Novartis acted with "intent" to withhold the sample, and that a sanction is warranted.

Third, Novartis argues complete foreclosure of its claim is a harsh penalty when MSN did not seek to compel production. (D.I. 1705 at 34). An adverse inference is a not complete foreclosure of Novartis' claim.

I think this adverse inference applies not just in relation to Noratech, but to MSN, too.

Novartis argues that the adverse inference should not apply to MSN's case. While true that MSN was not the party that sought production of Dr. Park's glassy solid, this is discovery common to both Defendants. Indeed, the Scheduling Order says, "The parties shall coordinate activities to reduce duplicative and cumulative discovery that is common to all Defendants." (D.I. 1098 at 5). Dr. Park created a Raman spectrum from her glassy solid that was used by Novartis to show that both Defendants' ANDAs infringe. The Defendants would have had their shared expert witness, Dr. McCreery, test Dr. Park's glassy solid. (Tr. 711:1–3; D.I. 1667 at 27:12–19). Novartis points out that MSN never made a glassy solid (*see* Tr. 397:4–6; D.I. 1705 at 34), but MSN wished to test Dr. Park's glassy solid, the material against which its ANDA was compared. I thus think it is appropriate to take an adverse inference against Novartis for failing to produce Dr. Park's glassy solid to Noratech.

In an analogous setting, the Ninth Circuit came to a similar conclusion. *See Payne v. Exxon Corp.*, 121 F.3d 503, 510 (9th Cir. 1997). In *Payne*, the Ninth Circuit affirmed the district court's dismissal of a case against two defendants as a sanction for the plaintiff failing to comply with a discovery order, even though only one of the defendants requested and filed a motion on

the discovery at issue. *Id.* at 507, 510. The court explained, "If Congress had intended to limit the district court's dismissal authority to claims against the party who propounded discovery, it would not have chosen such sweeping language [under Rule 37(b)(2)]."[11] *Id.* at 510. Further, "The district court could reasonably conclude that plaintiffs' failure to comply with court orders prejudiced both parties." *Id.* Here, Novartis' failure to produce Noratech's requested discovery prejudiced both defendants.

I will assume that, had Novartis produced the glassy solid sample to Defendants, it would have been unfavorable to Novartis' case. *See Gronquist v. Nicholas*, 2011 WL 4001103, at *8 (W.D. Wash. Aug. 12, 2011).

2. Infringement

Novartis must prove MSN's ANDA infringes by a preponderance of the evidence. *SmithKline*, 859 F.2d at 889. For all the foregoing reasons, I think Novartis did not. The reference Raman spectrum that Novartis used to compare to a Raman spectrum of MSN's ANDA is unreliable as a reference spectrum. Thus, an infringement analysis based on that "reference spectrum" is insufficient. The unreliability of Novartis' reference Raman spectrum, combined with an adverse inference due to Novartis' failure to produce the glassy solid sample reflected in the reference Raman spectrum, leads me to conclude that Novartis did not meet its burden to show MSN's ANDA infringes by a preponderance of the evidence.

IV. CONCLUSION

For the foregoing reasons, I find that Novartis did not prove that MSN's ANDA infringes by a preponderance of the evidence. I will enter a final judgment consistent with this opinion.

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[11] At issue here is a violation under Rule 37(c)(1), which allows for the sanctions listed in Rule 37(b)(2). FED. R. CIV. P. 37(c)(1)(C).

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

In re Entresto (Sacubitril/Valsartan) Patent Litigation	C.A. No. 20-2930-RGA
NOVARTIS PHARMACEUTICALS CORPORATION, Plaintiff, v. MSN PHARMACEUTICALS INC., MSN LABORATORIES PRIVATE LIMITED, MSN LIFE SCIENCES PRIVATE LIMITED, Defendants.	C.A. No. 22-1395-RGA

FINAL JUDGMENT AS TO
DEFENDANTS MSN PHARMACEUTICALS INC., MSN LABORATORIES PRIVATE LIMITED, AND MSN LIFE SCIENCES PRIVATE LIMITED

WHEREAS Plaintiff Novartis Pharmaceuticals Corporation ("Novartis") in the above-captioned suit has asserted that Defendants MSN Pharmaceuticals Inc., MSN Laboratories Private Limited, and MSN Life Sciences Private Limited (collectively "MSN" or "MSN Defendants") infringed claim 1 of Novartis's U.S. Patent No. 11,096,918 ("the '918 Patent") by filing Abbreviated New Drug Application ("ANDA") No. 213748;

WHEREAS Novartis has asserted that MSN's generic valsartan/sacubitril ANDA tablets identified in MSN's ANDA No. 213748 ("MSN's ANDA Products") infringe claim 1 of the '918 Patent;

WHEREAS MSN withdrew at trial its challenges to the validity of claim 1 of the '918 Patent;

WHEREAS the Court on July 11, 2025, issued a decision holding that the filing of MSN's ANDA No. 213748 and MSN's ANDA Products do not infringe claim 1 of the '918 Patent (Docket No. 20-md-2930, D.I. 1937; Docket No. 22-1395, D.I. 523);

WHEREAS the '918 Patent will expire the day after November 8, 2026;

IT IS HEREBY ORDERED, DECREED, AND ADJUDGED:

1. Judgment is entered in MSN's favor that MSN's filing of ANDA No. 213748, including any amendments or supplements thereto, does not infringe claim 1 of the '918 Patent under 35 U.S.C. § 271(e)(2).

2. Judgment is entered in MSN's favor that any use, sale, offer for sale, and/or manufacture within the United States, and/or importation into the United States of MSN's ANDA Products during the '918 Patent's term would not infringe claim 1 of the '918 Patent.

3. MSN's counterclaim that the '918 patent is invalid is dismissed with prejudice.

UNITED STATES DISTRICT JUDGE

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

In re Entresto (Sacubitril/Valsartan) Patent Litigation	Civil Action No. 20-md-2930-RGA
NOVARTIS PHARMACEUTICALS CORPORATION, Plaintiff, v. MSN PHARMACEUTICALS INC., MSN LABORATORIES PRIVATE LIMITED, MSN LIFE SCIENCES PRIVATE LIMITED, Defendants.	Civil Action No. 22-cv-1395-RGA

ORDER

For the reasons stated in the Trial Opinion (Docket No. 20-md-2930, D.I. 1937; Docket No. 22-1395, D.I. 523), Plaintiff has not shown by a preponderance of the evidence that Defendants infringe U.S. Patent No. 11,096,918. Plaintiff thus has not shown it is reasonably likely to succeed on the merits of proving infringement of the '918 patent on appeal. Plaintiff's Motion for Injunctive Relief (Docket No. 20-md-2930, D.I. 1882; Docket No. 22-1395, D.I. 483) is DENIED.

IT IS SO ORDERED.

Entered this 11th day of July, 2025

United States District Judge

US011096918B2

(12) **United States Patent**
Feng et al.

(10) **Patent No.: US 11,096,918 B2**
(45) **Date of Patent: *Aug. 24, 2021**

(54) **AMORPHOUS SOLID FORM OF COMPOUNDS CONTAINING S—N-VALERYL-N-{[2'-(1H-TETRAZOLE-5-YL)-BIPHENYL-4-YL]-METHYL}-VALINE AND (2R,4S)-5-BIPHENYL-4-YL-4-(3-CARBOXY-PROPIONYLAMINO)-2-METHYL-PENTANOIC ACID ETHYL ESTER MOIETIES AND SODIUM CATIONS**

(71) Applicant: **Novartis Pharmaceuticals Corporation**, East Hanover, NJ (US)

(72) Inventors: **Lili Feng**, Pine Brook, NJ (US); **Sven Erik Godtfredsen**, Chatham, NJ (US); **Paul Allen Sutton**, Getsville, NY (US); **Mahavir Prashad**, Montville, NJ (US); **Michael J. Girgis**, Montville, NJ (US); **Bin Hu**, Green Brook, NJ (US); **Yugang Liu**, Bridgewater, NJ (US); **Thomas J. Blacklock**, East Hanover, NJ (US); **Piotr Henryk Karpinski**, Lincoln Park, NJ (US)

(73) Assignee: **NOVARTIS PHARMACEUTICALS CORPORATION**, East Hanover, NJ (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **16/579,581**

(22) Filed: **Sep. 23, 2019**

(65) **Prior Publication Data**

US 2020/0016109 A1 Jan. 16, 2020

Related U.S. Application Data

(60) Continuation of application No. 16/006,252, filed on Jun. 12, 2018, now abandoned, which is a continuation of application No. 15/187,872, filed on Jun. 21, 2016, now abandoned, which is a division of application No. 14/311,788, filed on Jun. 23, 2014, now Pat. No. 9,388,134, which is a division of application No. 11/722,360, filed as application No. PCT/US2006/043710 on Nov. 8, 2006, now Pat. No. 8,877,938.

(60) Provisional application No. 60/822,086, filed on Aug. 11, 2006, provisional application No. 60/789,332, filed on Apr. 4, 2006, provisional application No. 60/735,541, filed on Nov. 10, 2005, provisional application No. 60/735,093, filed on Nov. 9, 2005.

(51) **Int. Cl.**

A61K 31/216	(2006.01)
A61K 31/41	(2006.01)
C07C 233/47	(2006.01)
C07D 257/04	(2006.01)
A61K 45/06	(2006.01)
A61K 31/4422	(2006.01)
A61K 31/5415	(2006.01)
C07D 207/50	(2006.01)

(52) **U.S. Cl.**

CPC ***A61K 31/216*** (2013.01); ***A61K 31/41*** (2013.01); ***A61K 31/4422*** (2013.01); ***A61K 31/5415*** (2013.01); ***A61K 45/06*** (2013.01); ***C07C 233/47*** (2013.01); ***C07D 207/50*** (2013.01); ***C07D 257/04*** (2013.01); *A61K 2300/00* (2013.01)

(58) **Field of Classification Search**

CPC C07C 233/47; C07D 257/04

See application file for complete search history.

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Primary Examiner — Timothy P Thomas

(57) **ABSTRACT**

An amorphous solid form of a compound comprising the angiotensin receptor antagonist (ARB) valsartan, the neutral endopeptidase inhibitor (NEPi) (2R,4S)-5-biphenyl-4-yl-4-(3-carboxy-propionylamino)-2-methylpentanoic acid ethyl ester and sodium cations is provided. This compound is useful for the treatment of hypertension and/or heart failure.

2 Claims, 1 Drawing Sheet

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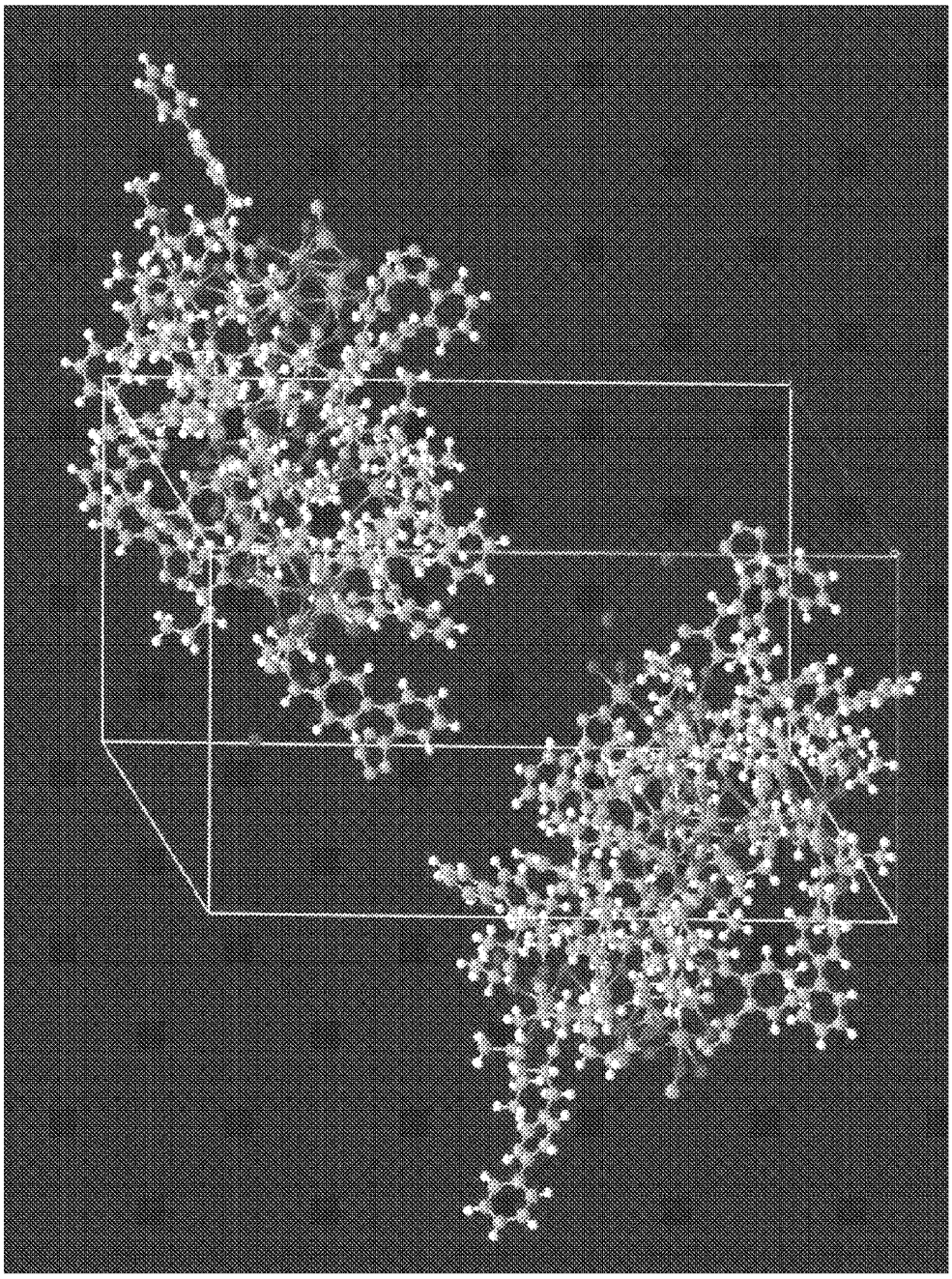


AMORPHOUS SOLID FORM OF COMPOUNDS CONTAINING S—N-VALERYL-N-{[2'-(1H-TETRAZOLE-5-YL)-BIPHENYL-4-YL]-METHYL}-VALINE AND (2R,4S)-5-BIPHENYL-4-YL-4-(3-CARBOXY-PROPIONYLAMINO)-2-METHYL-PENTANOIC ACID ETHYL ESTER MOIETIES AND SODIUM CATIONS

RELATED APPLICATIONS

This application is a continuation application of U.S. application Ser. No. 16/006,252, filed on Jun. 12, 2018, which is a continuation application of U.S. application Ser. No. 15/187,872, filed on Jun. 21, 2016, which is a divisional application of U.S. application Ser. No. 14/311,788, filed on Jun. 23, 2014, now U.S. Pat. No. 9,388,134, which is a divisional application of U.S. application Ser. No. 11/722,360, filed on Jan. 15, 2008, now U.S. Pat. No. 8,877,938, which is a national stage application, filed under 35 U.S.C. § 371, of International Application No. PCT/US06/43710, filed on Nov. 8, 2006, which claims the benefit of and priority to U.S. Provisional Application Nos. 60/822,086, filed Aug. 11, 2006, 60/789,332, filed Apr. 4, 2006, 60/735,541, filed on Nov. 10, 2005, and 60/735,093, filed on Nov. 9, 2005, the entire contents of each of which are incorporated herein by reference in their entireties.

FIELD OF THE INVENTION

The present invention is directed to dual-acting compounds and combinations of angiotensin receptor blockers and neutral endopeptidase inhibitors, in particular a dual acting molecule wherein the angiotensin receptor blocker and neutral endopeptidase inhibitor are linked via non-covalent bonding, or supramolecular complexes of angiotensin receptor blockers and neutral endopeptidase inhibitors, also described as linked pro-drugs, such as mixed salts or co-crystals, as well as to pharmaceutical combinations containing such a dual-acting compound or combination, methods of preparing such dual-acting compounds and methods of treating a subject with such a dual-acting compound or combination. Specifically, the invention is directed to a dual acting compound or supramolecular complex of two active agents having the same or different modes of action in one molecule.

BACKGROUND OF THE INVENTION

Angiotensin II is a hormone that causes blood vessels to constrict. This, in turn, can result in high blood pressure and strain on the heart. It is known that angiotensin II interacts with specific receptors on the surface of target cells. Two receptor subtypes for angiotensin II, namely AT1 and AT2, have been identified thus far. In recent times, great efforts have been made to identify substances that bind to the AT1 receptor. Angiotensin receptor blockers (ARBs, angiotensin II antagonists) are now known to prevent angiotensin II from binding to its receptors in the walls of blood vessels, thereby resulting in lower blood pressure. Because of the inhibition of the AT1 receptor, such antagonists can be used, therefore, as anti-hypertensives or for the treatment of congestive heart failure, among other indications.

Neutral endopeptidase (EC 3.4.24.11; enkephalinase; atriopeptidase; NEP) is a zinc-containing metalloprotease that cleaves a variety of peptide substrates on the amino side of hydrophobic residues [see Pharmacol Rev, Vol. 45, p. 87 (1993)]. Substrates for this enzyme include, but are not limited to, atrial natriuretic peptide (ANP, also known as ANF), brain natriuretic peptide (BNP), met- and leu-enkephalin, bradykinin, neurokinin A, endothelin-1 and substance P. ANP is a potent vasorelaxant and natriuretic agent [see J Hypertens, Vol. 19, p. 1923 (2001)]. Infusion of ANP in normal subjects resulted in a reproducible, marked enhancement of natriuresis and diuresis, including increases in fractional excretion of sodium, urinary flow rate and glomerular filtration rate [see J Clin Pharmacol, Vol. 27, p. 927 (1987)]. However, ANP has a short half-life in circulation, and NEP in kidney cortex membranes has been shown to be the major enzyme responsible for degrading this peptide [see Peptides, Vol. 9, p. 173 (1988)]. Thus, inhibitors of NEP (neutral endopeptidase inhibitors, NEPi) should increase plasma levels of ANP and, hence, are expected to induce natriuretic and diuretic effects.

While substances, such as angiotensin receptor blockers and neutral endopeptidase inhibitors may be useful in the control of hypertension, essential hypertension is a polygenic disease and is not always controlled adequately by monotherapy. Approximately 333 million adults in economically developed countries and about 65 million Americans (1 in 3 adults) had high blood pressure in 2000 [see Lancet, Vol. 365, p. 217 (2005); and Hypertension, Vol. 44, p. 398 (2004)]. Prolonged and uncontrolled hypertensive vascular disease ultimately leads to a variety of pathological changes in target organs, such as the heart and kidney.

Sustained hypertension can lead as well to an increased occurrence of stroke. Therefore, there is a strong need to evaluate the efficacy of anti-hypertensive therapy, an examination of additional cardiovascular endpoints, beyond those of blood pressure lowering, to get further insight into the benefits of combined treatment.

The nature of hypertensive vascular diseases is multifactorial. Under certain circumstances, drugs with different mechanisms of action have been combined. However, just considering any combination of drugs having different modes of action does not necessarily lead to combinations with advantageous effects. Accordingly, there is a need for efficacious combination therapy which does not have deleterious side effects.

SUMMARY OF THE INVENTION

In a first aspect, the present invention is directed to a dual-acting compound, such as a supramolecular complex, comprising:

(a) an angiotensin receptor antagonist;
(b) a neutral endopeptidase inhibitor (NEPi); and optionally
(c) a pharmaceutically acceptable cation.

The present invention is also directed to a dual-acting compound, such as a supramolecular complex, obtainable by:

(i) dissolving an angiotensin receptor antagonist and a neutral endopeptidase inhibitor (NEPi) in a suitable solvent;
(ii) dissolving a basic compound of Cat in a suitable solvent, whercin Cat is a cation;
(iii) combining the solutions obtained in steps (i) and (ii);
(iv) precipitation of the solid, and drying same to obtain the dual-acting compound; or alternatively obtaining the dual-acting compound by exchanging the solvent(s) employed in steps (i) and (ii) by
(iva) evaporating the resulting solution to dryness;
(va) re-dissolving the solid in a suitable solvent;

(via) precipitation of the solid and drying same to obtain the dual-acting compound.

The present invention is also directed to linked pro-drugs comprising:

(a) an angiotensin receptor antagonist or a pharmaceutically acceptable salt thereof; and

(b) a NEPi or a pharmaceutically acceptable salt thereof, wherein the angiotensin receptor antagonist or a pharmaceutically acceptable salt thereof and the NEPi or a pharmaceutically acceptable salt thereof are linked by a linking moiety.

The present invention is also directed to a combination comprising:

(a) a pharmaceutically acceptable salt of an angiotensin receptor antagonist; and

(b) a pharmaceutically acceptable salt of a neutral endopeptidase inhibitor (NEPi);

wherein the pharmaceutically acceptable salt of the angiotensin receptor antagonist and the NEPi is the same and is selected from a salt of Na, K or NH_4.

In preferred embodiments, the angiotensin receptor antagonist and NEPi have acidic groups which facilitate formation of the dual acting compound, such as the supramolecular complex of the present invention.

Preferably, the angiotensin receptor antagonist is selected from the group consisting of valsartan, losartan, irbesartan, telmisartan, eprosartan, candesartan, olmesartan, saprisartan, tasosartan, elisartan and combinations thereof.

In preferred embodiments, the NEPi is selected from the group consisting of: SQ 28,603; N—[N-[1(S)-carboxyl-3-phenylpropyl]-(S)-phenylalanyl]-(S)-isoserine; N—[N-[((1S)-carboxy-2-phenyl)ethyl]-(S)-phenylalanyl]-β-alanine; N-[2(S)-mercaptomethyl-3-(2-methylphenyl)-propionyl]methionine; (cis-4-[[[1-[2-carboxy-3-(2-methoxyethoxy)propyl]-cyclopentyl]carbonyl]amino]-cyclohexanecarboxylic acid); thiorphan; retro-thiorphan; phosphoramidon; SQ 29072; N-(3-carboxy-1-oxopropyl)-(4S)-p-phenylphenylmethyl)-4-amino-2R-methylbutanoic acid ethyl ester; (S)-cis-4-[1-[2-(5-indanyloxycarbonyl)-3-(2-methoxyethoxy)propyl]-1-cyclopentanecarboxamido]-1-cyclohexanecarboxylic acid; 3-(1-[6-endo-hydroxymethyl-bicyclo[2,2,1]heptane-2-exo-carbamoyl]cyclopentyl)-2-(2-methoxyethyl)propanoic acid; N-(1-(3-(N-t-butoxycarbonyl-(S)-prolylamino)-2(S)-t-butoxy-carbonylpropyl)cyclopentanecarbonyl)-O-benzyl-(S)-serine methyl ester; 4-[[2-(mercaptomethyl)-1-oxo-3-phenylpropyl]amino]benzoic acid; 3-[1-(cis-4-carboxycarbonyl-cis-3-butylcyclohexyl-r-1-carbamoyl)cyclopentyl]-2S-(2-methoxyethoxymethyl)propanoic acid; N-((2S)-2-(4-biphenylmethyl)-4-carboxy-5-phenoxyvaleryl)glycine; N-(1-(N-hydroxycarbamoylmethyl)-1-cyclopentanecarbonyl)-L-phenylalanine; (S)-(2-biphenyl-4-yl)-1-(1H-tetrazol-5-yl)ethylamino) methylphosphonic acid; (S)-5-(N-(2-(phosphonomethylamino)-3-(4-biphenyl)propionyl)-2-aminoethyl)tetrazole; β-alanine; 3-[1,1'-biphenyl]-4-yl-N-[diphenoxyphosphinyl)methyl]-L-alanyl; N-(2-carboxy-4-thienyl)-3-mercapto-2-benzylpropanamide; 2-(2-mercaptomethyl-3-phenylpropionamido)thiazol-4-ylcarboxylic acid; (L)-(1-((2,2-dimethyl-1,3-dioxolan-4-yl)-methoxy)carbonyl)-2-phenylethyl)-L-phenylalanyl)-β-alanine; N—[N-[(L)-[1-[(2,2-dimethyl-1,3-dioxolan-4-yl)-methoxy]carbonyl]-2-phenylethyl]-L-phenylalanyl]-(R)-alanine; N—[N-[(L)-1-carboxy-2-phenylethyl]-L-phenylalanyl]-(R)-alanine; N-[2-acetylthiomethyl-3-(2-methyl-phenyl)propionyl]-methionine ethyl ester; N-[2-mercaptomethyl-3-(2-methylphenyl)propionyl]-methionine; N-[2(S)-mercaptomethyl-3-(2-methylphenyl)propanoyl]-(S)-isoserine; N—(S)-[3-mercapto-2-(2-methylphenyl)propionyl]-(S)-2-methoxy-(R)-alanine; N-[1-[[1(S)-benzyloxy-carbonyl-3-phenylpropyl]amino]cyclopentylcarbonyl]-(S)-isoserine: N-[1-[[1(S)-carbonyl-3-phenylpropyl]amino]-cyclopentylcarbonyl]-(S)-isoserine; 1,1'-[dithiobis-[2(S)-(2-methylbenzyl)-1-oxo-3,1-propanediyl]]-bis-(S)-isoserine; 1,1'-[dithiobis-[2(S)-(2-methylbenzyl)-1-oxo-3,1-propanediyl]]-bis-(S)-methionine; N-(3-phenyl-2-(mercaptomethyl)-propionyl)-(S)-4-(methylmercapto)methionine; N-[2-acetylthiomethyl-3-phenyl-propionyl]-3-aminobenzoic acid; N-[2-mercaptomethyl-3-phenyl-propionyl]-3-aminobenzoic acid; N-[1-(2-carboxy-4-phenylbutyl)-cyclopentane-carbonyl]-(S)-isoserine; N-[1-(acetylthiomethyl)cyclopentane-carbonyl]-(S)-methionine ethyl ester; 3(S)-[2-(acetylthiomethyl)-3-phenyl-propionyl]amimo-ε-caprolactam; N-(2-acetylthiomethyl-3-(2-methylphenyl) propionyl)-methionine ethyl ester; and combinations thereof. Preferably, the dual-acting compound or combination, in particular the supramolecular complex, is a mixed salt or a co-crystal. It is also preferred that the linked pro-drug is a mixed salt or a co-crystal.

In a second aspect, the present invention is directed to pharmaceutical composition comprising

(a) the aforementioned dual-acting compound or combination, such as the aforementioned complex; and

(b) at least one pharmaceutically acceptable additive.

The present invention is also directed to pharmaceutical compositions comprising a linked pro-drug comprising:

(a) an angiotensin receptor antagonist or a pharmaceutically acceptable salt thereof;

(b) a NEPi or a pharmaceutically acceptable salt thereof, wherein the angiotensin receptor antagonist or a pharmaceutically acceptable salt thereof and the NEPi or a pharmaceutically acceptable salt thereof are linked by a linking moiety; and

(c) at least one pharmaceutically acceptable additive.

In a third aspect, the present invention is directed to a method of preparing a dual-acting compound, in particular a supramolecular complex, comprising

(a) an angiotensin receptor antagonist;

(b) a neutral endopeptidase inhibitor (NEPi); and optionally

(c) a pharmaceutically acceptable cation selected from the group consisting of Na, K and NH_4;

said method comprising the steps of:

(i) dissolving an angiotensin receptor antagonist and a neutral endopeptidase inhibitor (NEPi) in a suitable solvent;

(ii) dissolving a basic compound of Cat in a suitable solvent, wherein Cat is a cation;

(iii) combining the solutions obtained in steps (i) and (ii);

(iv) precipitation of the solid, and drying same to obtain the dual-acting compound; or alternatively obtaining the dual-acting compound by exchanging the solvent(s) employed in steps (i) and (ii) by

(iva) evaporating the resulting solution to dryness;

(va) re-dissolving the solid in a suitable solvent;

(via) precipitation of the solid and drying same to obtain the dual-acting compound.

The present invention is also directed to a method of making a linked pro-drug comprising:

(a) an angiotensin receptor antagonist or a pharmaceutically acceptable salt thereof;

(b) a NEPi or a pharmaceutically acceptable salt thereof, wherein the angiotensin receptor antagonist or a pharmaceutically acceptable salt thereof and the NEPi or a pharmaceutically acceptable salt thereof are linked by

a linking moiety; and comprising adding a linking moiety and a solvent to a mixture of an angiotensin receptor antagonist and a NEPi; and

(d) isolating the linked pro-drug.

In a fourth aspect, this invention is directed to a method of treating or preventing a disease or condition, such as hypertension, heart failure (acute and chronic), congestive heart failure, left ventricular dysfunction and hypertrophic cardiomyopathy, diabetic cardiac myopathy, supraventricular and ventricular arrhythmias, atrial fibrillation, atrial flutter, detrimental vascular remodeling, myocardial infarction and its sequelae, atherosclerosis, angina (unstable or stable), renal insufficiency (diabetic and non-diabetic), heart failure, angina pectoris, diabetes, secondary aldosteronism, primary and secondary pulmonary hypertension, renal failure conditions, such as diabetic nephropathy, glomerulonephritis, scleroderma, glomerular sclerosis, proteinuria of primary renal disease, and also renal vascular hypertension, diabetic retinopathy, other vascular disorders, such as migraine, peripheral vascular disease, Raynaud's disease, luminal hyperplasia, cognitive dysfunction (such as Alzheimer's), glaucoma and stroke comprising administering the afore-mentioned dual-acting compound or combination, in particular the supramolecular complex, or the afore-mentioned linked pro-drug, preferably, the complex, to a subject in need of such treatment.

BRIEF DESCRIPTION OF THE DRAWING

FIG. 1 shows a pictorial representation of the unit cell of the supramolecular complex of trisodium [3-((1 S,3R) −1-biphenyl-4-y lmethyl-3-ethoxy carbonyl-1-butylcarbamoyl)propionate-(S)-3 '-methyl-2'-(pentanoyl {2 "-(tetrazol-5-ylate)biphenyl-4'-y 'methyl} amino)butyrate] hemipentahydrate comprising two asymmetric units. The following color code is used: grey=carbon atom; blue=nitrogen atom; red=oxygen atom; violet=sodium atom.

DETAILED DESCRIPTION

The present invention relates to a dual-acting compound or combination, in particular a supramolecular complex, or linked pro-drug or in particular a supramolecular complex of two active agents with different mechanisms of action, namely an angiotensin receptor antagonist and a neutral endopeptidase inhibitor, which can form a unique molecular entity for the treatment of patients with various cardiovascular and/or renal diseases.

One embodiment of the invention is directed to a physical combination comprising:

(a) a pharmaceutically acceptable salt of an angiotensin receptor antagonist; and

(b) a pharmaceutically acceptable salt of a neutral endopeptidase inhibitor (NEPi); wherein the pharmaceutically acceptable salt of the angiotensin receptor antagonist and the NEPi is the same and is selected from a salt of Na, K or NH_4.

Specifically, it is preferred that the two active agents are combined with each other so as to form a single dual-acting compound, in particular a supramolecular complex. By doing so, a new molecular or supramolecular entity is formed having distinct properties different to the above physical combination.

Thus, the present invention is directed to a dual-acting compound, in particular a supramolecular complex, comprising:

(a) an angiotensin receptor antagonist;

(b) a neutral endopeptidase inhibitor (NEPi); and

(c) a pharmaceutically acceptable cation preferably selected from the group consisting of Na, K and NH_4.

The present invention is also directed to a dual-acting compound, in particular a supramolecular complex, obtainable by:

(i) dissolving an angiotensin receptor antagonist and a neutral endopeptidase inhibitor (NEPi) in a suitable solvent;

(ii) dissolving a basic compound of Cat such as (Cat)OH, $(Cat)_2CO_3$, $(Cat)HCO_3$ in a suitable solvent, wherein Cat is a cation preferably selected from the group consisting of Na, K and NH_4;

(iii) combining the solutions obtained in steps (i) and (ii);

(iv) precipitation of the solid, and drying same to obtain the dual-acting compound; or alternatively obtaining the dual-acting compound by exchanging the solvent(s) employed in steps (i) and (ii) by

(iva) evaporating the resulting solution to dryness;

(va) re-dissolving the solid in a suitable solvent;

(via) precipitation of the solid and drying same to obtain the dual-acting compound.

The present invention is further directed to linked pro-drugs comprising:

(a) an angiotensin receptor antagonist or a pharmaceutically acceptable salt thereof; and

(b) a NEPi or a pharmaceutically acceptable salt thereof, wherein the angiotensin receptor antagonist or a pharmaceutically acceptable salt thereof and the NEPi or a pharmaceutically acceptable salt thereof are linked by a linking moiety.

The two components are each linked to a linking moiety thereby creating a linked pro-drug.

Preferably, the linked pro-drug is substantially pure; as used herein, "substantially pure" refers to at least 90%, more preferably at least 95% and most preferably at least 98% purity.

As one preferred embodiment of the present invention, the linked pro-drug has a structure such that by linking the two components with the linking moiety, a supramolecular complex is formed.

For the purpose of the present invention, the term "dual-acting compound" is intended to describe that these compounds have two different modes of action in one compound, one is the angiotensin receptor blockade resulting from the ARB molecular moiety of the compound and the other is the neutral endopeptidase inhibition resulting from the NEPi molecular moiety of the compound.

For the purpose of the present invention, the term "compound" is intended to describe a chemical substance comprising covalent bonds within the two pharmaceutically active agents, the ARB and the NEPi molecular moieties, and non-covalent interactions between these two pharmaceutically active agents, the ARB and the NEPi molecular moieties.

Typically, hydrogen bonding can be observed between the two pharmaceutically active agents, the ARB and the NEPi molecular moieties. Ionic bonds can be present between the cation and one or both of the two pharmaceutically active agents, the ARB and the NEPi molecular moieties. Other types of bonds may also be present within the compound

such as van der Waals forces. For illustrative purposes, the dual-acting compound of the present invention could be represented as follows:

$$(ARB)\text{-}(L)_m\text{-}(NEPi)$$

wherein L is a linking moiety, such as a cation or is a noncovalent bond and m is an integer from 1 or more. In other words the ARB and NEPi moiety can be connected via non-covalent bonds such as hydrogen bonding. Alternatively or additionally they may be connected via a linking moiety such as a cation.

In one embodiment, the dual-acting compound may be considered to be a linked pro-drug, whereby the linking moiety, such as the cation, linking the two pharmaceutically active agents, the ARB and the NEPi, forms the pro-drug of these agents which are released once the linked pro-drug is ingested and absorbed.

In a preferred embodiment, the dual-acting compound is a complex, in particular a supramolecular complex.

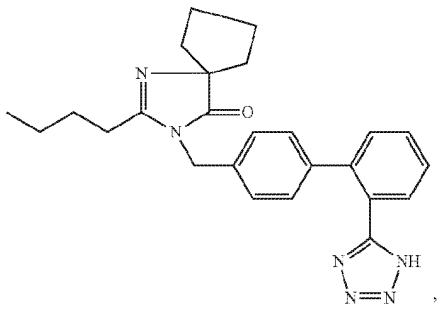
For the purpose of the present invention, the term "supramolecular complex" is intended to describe an interaction between the two pharmaceutically active agents, the cations and any other entity present such as a solvent, in particular water, by means of noncovalent, intermolecular bonding between them. This interaction leads to an association of the species present in the supramolecular complex distinguishing this complex over a physical mixture of the species.

The noncovalent intermolecular bonding can be any interactions known in the art to form such supramolecular complexes, such as hydrogen bonding, van der Waals forces and π-π stacking. Ionic bonds can also be present. Preferably, there exists ionic bonding and additionally hydrogen bonding to form a network of interactions within the complex. The supramolecular complex exists preferably in the solid state but may also be present in liquid media. As a preferred embodiment of the invention, the complex is crystalline and in this case is preferably a mixed crystal or co-crystal.

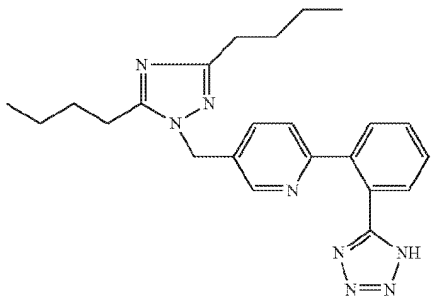
Typically, the dual-acting compound, in particular the supramolecular complex shows properties such as melting point, IR spectrum etc. that are different from a physical mixture of the species.

Preferably, the dual-acting compound, in particular the supramolecular complex, has a network of non-covalent bonds, in particular hydrogen bonds, between the two pharmaceutically active agents and any solvent, if present, preferably water. Moreover, it is preferred that the dual-acting compound, in particular the supramolecular complex, has a network of non-covalent bonds, in particular ionic and hydrogen bonds, between the two pharmaceutically active agents, the cation and any solvent, if present, preferably water. The cation is preferably coordinated to several oxygen ligands, thus, providing a linkage between these oxygen ligands. The oxygen ligands come from the carbonyl and carboxylate groups present in the two pharmaceutically active agents and preferably also from any solvent, if present, preferably water.

The dual acting compound comprises a molecular moiety of an angiotensin receptor antagonist. This means that a molecular moiety derived from an angiotensin receptor antagonist is participating in the build-up of the dual-acting compound. The angiotensin receptor antagonist is part of the compound and connected to the NEP inhibitor directly or indirectly via non-covalent bonds. For sake of convenience, throughout the application, the term "angiotensin receptor antagonist" will be used when describing this part of the compound. Angiotensin receptor antagonists (ARBs) suitable for use in the present invention include, without limitation, valsartan, losartan, irbesartan, telmisartan, eprosartan, candesartan, olmesartan saprisartan, tasosartan, elisartan, the compound with the designation E-1477 of the following formula

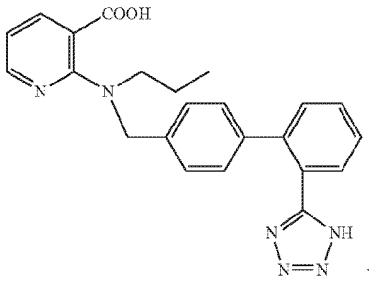


the compound with the designation SC-52458 of the following formula



and

the compound with the designation the compound ZD-8731 of the following formula



Suitable angiotensin II receptor antagonist also includes, but is not limited to, saralasin acetate, candesartan cilexetil, CGP-63170, EMD-66397, KT3-671, LR-B/081, valsartan, A-81282, BIBR-363, BIBS-222, BMS-184698, candesartan, CV-11194, EXP-3174, KW-3433, L-161177, L-162154, LR-B/057, LY-235656, PD-150304, U-96849, U-97018, UP-275-22, WAY-126227, WK-1492.2K, YM-31472, losartan potassium, E-4177, EMD-73495, eprosartan, HN-65021, irbesartan, L-159282, ME-3221, SL-91.0102, Tasosartan, Telmisartan, UP-269-6, YM-358, CGP-49870, GA-0056,

L-159689, L-162234, L-162441, L-163007, PD-123177, A-81988, BMS-180560, CGP-38560A, CGP-48369, DA-2079, DE-3489, DuP-167, EXP-063, EXP-6155, EXP-6803, EXP-7711, EXP-9270, FK-739, HR-720, ICI-D6888, ICI-D7155, ICI-D8731, isoteoline, KRI-1177, L-158809, L-158978, L-159874, LR B087, LY-285434, LY-302289, LY-315995, RG-13647, RWJ-38970, RWJ-46458, S-8307, S-8308, saprisartan, saralasin, Sarmesin, WK-1360, X-6803, ZD-6888, ZD-7155, ZD-8731, BIBS39, CI-996, DMP-811, DuP-532, EXP-929, L-163017, LY-301875, XH-148, XR-510, zolasartan and PD-123319.

Also included within the scope of this aspect of the invention are combinations of the above-identified ARBs.

ARBs to be used for preparing the combination or complex in accordance with the present invention can be purchased from commercial sources or can be prepared according to known methods. ARBs may be used for purposes of this invention in their free form, as well as in any suitable salt or ester form.

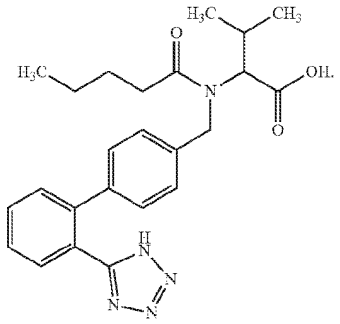
Preferred salts forms include acid addition salts. The compounds having at least one acid group (e.g., COOH or 5-tetrazolyl) can also form salts with bases. Suitable salts with bases are, e.g., metal salts, such as alkali metal or alkaline earth metal salts, e.g., sodium, potassium, calcium or magnesium salts, or salts with ammonia or an organic amine, such as morpholine, thiomorpholine, piperidine, pyrrolidine, a mono-, di- or tri-lower alkylamine, e.g., ethyl-, tert-butyl-, diethyl-, diisopropyl-, triethyl-, tributyl- or dimethylpropylamine, or a mono-, di- or trihydroxy lower alkylamine, e.g., mono-, di- or tri-ethanolamine. Corresponding internal salts may furthermore be formed. Salts which are unsuitable for pharmaceutical uses but which can be employed, e.g., for the isolation or purification of free compounds I or their pharmaceutically acceptable salts, are also included. Even more preferred salts are, e.g., selected from the mono-sodium salt in amorphous form; di-sodium salt of valsartan in amorphous or crystalline form, especially in hydrate form, thereof.

Mono-potassium salt of valsartan in amorphous form; di-potassium salt of valsartan in amorphous or crystalline form, especially in hydrate form, thereof.

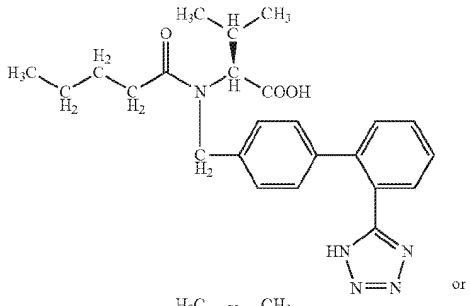
Calcium salt of valsartan in crystalline form, especially in hydrate form, primarily the tetrahydrate thereof; magnesium salt of valsartan in crystalline form, especially in hydrate form, primarily the hexahydrate thereof; calcium/magnesium mixed salt of valsartan in crystalline form, especially in hydrate form; bis-diethylammonium salt of valsartan in crystalline form, especially in hydrate form; bis-dipropylammonium salt of valsartan in crystalline form, especially in hydrate form; bis-dibutylammonium salt of valsartan in crystalline form, especially in hydrate form, primarily the hemihydrate thereof; mono-L-arginine salt of valsartan in amorphous form; bis-L-arginine salt of valsartan in amorphous form; mono-L-lysine salt of valsartan in amorphous form; bis-L-lysine salt of valsartan in amorphous form.

Preferably when preparing the dual-acting compound, in particular the complex according to the present invention, the free form of the ARB is used.

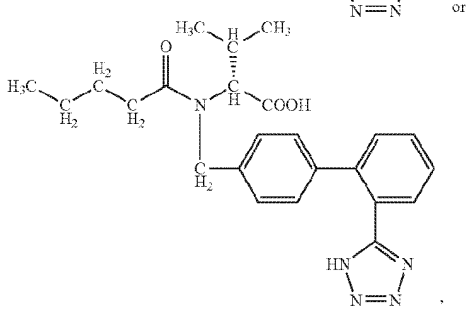
In a preferred embodiment of this invention, the angiotensin receptor blocker used in the combination or complex of the present invention is Valsartan the molecular structure of which is shown below



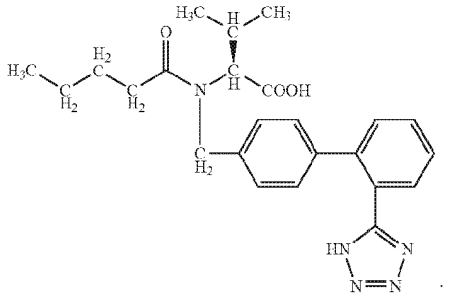
Valsartan may be in the racemic form or as one of the two isomers shown below



or



preferably



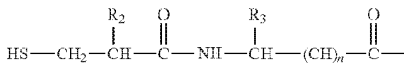
Valsartan ((S)—N-valeryl-N-{[2'-(1H-tetrazole-5-yl)-biphenyl-4-yl]-methyl}-valine) used according to the present invention can be purchased from commercial sources or can be prepared according to known methods. For example, the preparation of valsartan is described in U.S. Pat. No. 5,399,578 and EP 0 443 983, the entire disclosure of each of which is incorporated by reference herein. Valsartan may be used for purposes of this invention in its free acid form, as well as in any suitable salt form. Additionally, esters or other derivatives of the carboxylic grouping may be applied for the synthesis of linked pro-drugs, as well as salts and derivatives of the tetrazole grouping. Reference to ARBs includes reference to pharmaceutically acceptable salts thereof.

Preferably, the ARB is a diprotic acid. Thus, the angiotensin receptor blocker has a charge of 0, 1 or 2 depending on the pH of the solution.

In the combination of the present invention, the ARB is in the form of a pharmaceutically acceptable salt selected from Na, K or NH_4, preferably Na. This includes both the mono- and di-salt of these cations, preferably the di-salt. In particular in the case of valsartan this means that both the carboxylic acid moiety and the tetrazole moiety form the salt.

In the dual-acting compound, in particular the supramolecular complex of the present invention, typically the free form of the ARB is employed in the preparation and the cationic species present in the complex is introduced by using a base, e.g. (Cat)OH.

The dual acting compound comprises a molecular moiety of a neutral endopeptidase inhibitor. This means that a molecular moiety derived from a neutral endopeptidase inhibitor is participating in the build-up of the dual-acting compound. The neutral endopeptidase inhibitor is part of the compound and connected to the ARB directly or indirectly via non-covalent bonds. For sake of convenience, throughout the application, the term "neutral endopeptidase inhibitor" will be used when describing this part of the compound. Neutral endopeptidase inhibitors suitable for use in the present invention include those of formula (I)



(I)

wherein

R_2 is alkyl of 1-7 carbons, trifluoromethyl, phenyl, substituted phenyl, —(CH_2)1 to 4-phenyl, or —(CH_2)1 to 4-substituted phenyl;

R_3 is hydrogen, alkyl of 1-7 carbons, phenyl, substituted phenyl, —(CH_2)1 to 4-phenyl or —(CH_2)1 to 4-substituted phenyl;

R_1 is hydroxy, alkoxy of 1-7 carbons or NH_2;

n is an integer from 1-15;

and the term substituted phenyl refers to a substituent selected from lower alkyl of 1-4 carbons, lower alkoxy of 1-4 carbons, lower alkylthio of 1-4 carbons, hydroxy, Cl, Br or F.

Preferred neutral endopeptidase inhibitors of formula (I) include compounds,

wherein

R_2 is benzyl;

R_3 is hydrogen;

n is an integer from 1-9; and

R_1 is hydroxy.

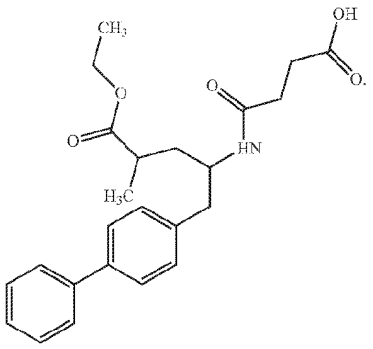
Another preferred neutral endopeptidase inhibitor is (3S,2'R)-3-{1-[2'-(ethoxycarbonyl)-4'-phenyl-butyl]-cyclopentan-1-carbonylamino}-2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepine-1-acetic acid or a pharmaceutically acceptable salt thereof.

Preferred neutral endopeptidase inhibitors suitable for use in the present invention include, without limitation, SQ 28,603; N—[N-[1(S)-carboxyl-3-phenylpropyl]-(S)-phenylalanyl]-(S)-isoserine; N—[N-[((1S)-carboxy-2-phenyl)ethyl]-(S)-phenylalanyl]-β-alanine; N-[2(S)-mercaptomethyl-3-(2-methylphenyl)-propionyl]methionine; (cis-4-[[[1-[2-carboxy-3-(2-methoxyethoxy)propyl]-cyclopentyl]carbonyl]amino]-cyclohexanecarboxylic acid); thiorphan; retro-thiorphan; phosphoramidon; SQ 29072; (2R,4S)-5-biphenyl-4-yl-4-(3-carboxy-propionylamino)-2-methylpentanoic acid ethyl ester; N-(3-carboxy-1-oxopropyl)-(4S)-p-phenylphenylmethyl)-4-amino-2R-methylbutanoic acid; (S)-cis-4-[1-[2-(5-indanyloxycarbonyl)-3-(2-methoxyethoxy)propyl]-1-cyclopentanecarboxamido]-1-cyclohexanecarboxylic acid; 3-(1-[6-endo-hydroxymethylbicyclo[2,2,1]heptane-2-exo-carbamoyl]cyclopentyl)-2-(2-methoxyethyl)propanoic acid; N-(1-(3-(N-t-butoxycarbonyl-(S)-prolylamino)-2(S)-t-butoxycarbonylpropyl)cyclopentanecarbonyl)-O-benzyl-(S)-serine methyl ester; 4-[[2-(mercaptomethyl)-1-oxo-3-phenylpropyl]amino]benzoic acid; 3-[1-(cis-4-carboxycarbonyl-cis-3-butylcyclohexyl-r-1-carbamoyl)cyclopentyl]-2S-(2-methoxyethoxymethyl)propanoic acid; N-((2S)-2-(4-biphenylmethyl)-4-carboxy-5-phenoxyvaleryl)glycine; N-(1-(N-hydroxycarbamoylmethyl)-1-cyclopentanecarbonyl)-L-phenylalanine; (S)-(2-biphenyl-4-yl)-1-(1H-tetrazol-5-yl)ethylamino) methylphosphonic acid; (S)-5-(N-(2-(phosphonomethylamino)-3-(4-biphenyl)propionyl)-2-aminoethyl)tetrazole; β-alanine; 3-[1,1'-biphenyl]-4-yl-N-[diphenoxyphosphinyl)methyl]-L-alanyl; N-(2-carboxy-4-thienyl)-3-mercapto-2-benzylpropanamide; 2-(2-mercaptomethyl-3-phenylpropionamido)thiazol-4-ylcarboxylic acid; (L)-(1-((2,2-dimethyl-1,3-dioxolan-4-yl)-methoxy)carbonyl)-2-phenylethyl)-L-phenylalanyl)-β-alanine; N—[N-[(L)-[1-[(2,2-dimethyl-1,3-dioxolan-4-yl)-methoxy]carbonyl]-2-phenylethyl]-L-phenylalanyl]-(R)-alanine; N—[N-[(L)-1-carboxy-2-phenylethyl]-L-phenylalanyl]-(R)-alanine; N-[2-acetylthiomethyl-3-(2-methyl-phenyl)propionyl]-methionine ethyl ester; N-[2-mercaptomethyl-3-(2-methylphenyl)propionyl]-methionine; N-[2(S)-mercaptomethyl-3-(2-methylphenyl)propanoyl]-(S)-isoserine: N—(S)-[3-mercapto-2-(2-methylphenyl)propionyl]-(S)-2-methoxy-(R)-alanine; N-[1-[[1(S)-benzyloxycarbonyl-3-phenylpropyl]amino]cyclopentylcarbonyl]-(S)-isoserine; N-[1-[[1(S)-carbonyl-3-phenylpropyl]amino]-cyclopentylcarbonyl]-(S)-isoserine; 1,1'-[dithiobis-[2(S)-(2-methylbenzyl)-1-oxo-3,1-propanediyl]]-bis-(S)-isoserine; 1,1'-[dithiobis-[2(S)-(2-methylbenzyl)-1-oxo-3,1-propanediyl]]-bis-(S)-methionine; N-(3-phenyl-2-(mercaptom-

ethyl)-propionyl)-(S)-4-(methylmercapto)methionine; N-[2-acetylthiomethyl-3-phenyl-propionyl]-3-aminobenzoic acid; N-[2-mercaptomethyl-3-phenyl-propionyl]-3-aminobenzoic acid; N-[1-(2-carboxy-4-phenylbutyl)-cyclopentane-carbonyl]-(S)-isoserine; N-[1-(acetylthiomethyl)cyclopentane-carbonyl]-(S)-methionine ethyl ester; 3(S)-[2-(acetylthiomethyl)-3-phenyl-propionyl]amimo-ε-caprolactam; N-(2-acetylthiomethyl-3-(2-methylphenyl) propionyl)-methionine ethyl ester; and combinations thereof.

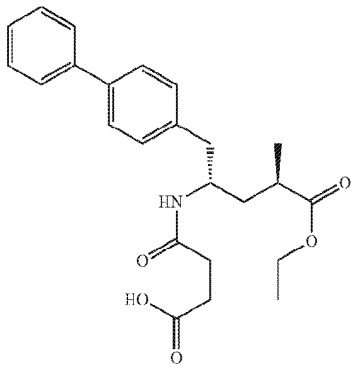
Neutral endopeptidase inhibitors can be purchased from commercial sources or can be prepared according to known methods, such as those set forth in any of U.S. Pat. Nos. 4,722,810, 5,223,516, 4,610,816, 4,929,641, South African Patent Application 84/0670, UK 69578, U.S. Pat. No. 5,217,996, EP 00342850, GB 02218983, WO 92/14706, EP 00343911, JP 06234754, EP 00361365, WO 90/09374, JP 07157459, WO 94/15908, U.S. Pat. Nos. 5,273,990, 5,294,632, 5,250,522, EP 00636621, WO 93/09101, EP 00590442, WO 93/10773, U.S. Pat. No. 5,217,996, the disclosure of each of which is incorporated by reference. Neutral endopeptidase inhibitors may be used for purposes of this invention in their free form, as well as in any suitable salt form. Reference to neutral endopeptidase inhibitors includes reference to pharmaceutically acceptable salts thereof.

Additionally esters or other derivatives of any carboxylic grouping may be applied for the synthesis of linked pro-drugs, as well as salts and derivatives of any other acidic grouping. In a preferred embodiment of this invention, the NEPi is 5-biphenyl-4-yl-4-(3-carboxy-priopionylamino)-2-methyl-pentanoic acid ethyl ester of formula (II) or the respective hydrolysed form 5-biphenyl-4-yl-4-(3-carboxy-priopionylamino)-2-methyl-pentanoic acid.



(II)

The compound of formula (II) can exist as the (2R,4S), (2R,4S), (2R,4S) or (2R,4S) isomer. Preferred is (2R,4S)-5-biphenyl-4-yl-4-(3-carboxy-propionylamino)-2-methyl-pentanoic acid ethyl ester as shown below:



The compound of formula (II) is a specific inhibitor of NEP and is described in U.S. Pat. No. 5,217,996. It can be purchased from commercial sources or can be prepared according to known methods. The compound of formula (II) may be used for purposes of this invention in its free form, as well as in any suitable salt or ester form.

Preferably the NEPi is a monoprotic acid. Thus, the NEPi has a charge of 0 or 1 depending on the pH of the solution.

In the combination of the present invention, the NEPi is in the form of a pharmaceutically acceptable salt selected from Na, K or NH_4, preferably Na.

In the dual-acting compound, in particular the supramolecular complex of the present invention, typically the free form of the NEPi is employed in the preparation and the cationic species present in the complex is introduced by using a base, (Cat)OH.

The dual acting compound preferably comprises non-covalent bonds between the ARB and the NEPi. Alternatively or in addition, it optionally comprises a linking moiety such as a pharmaceutically acceptable cation.

The linking moiety includes, but is not limited to, generally regarded as safe (GRAS) compounds or other pharmacologically acceptable compounds. The linking moiety may be an ion or a neutral molecule. In the case wherein the linking moiety is an ion the linked pro-drug is a salt and when the linking moiety is a neutral molecule the linked pro-drug is a co-crystal. Without being bound by any particular theory, the acidic portion of the ARB and NEPi donate a proton to the basic linking moiety such that all three components then become united to form one molecule. When the linked pro-drug is ingested by the subject intended to be treated the more acidic nature of the ingestion environment causes the linked pro-drug to separate into individual components concomitant with ingestion and absorption and therefore be converted into active agents to provide their beneficial biological action to treat the intended diseases.

In the case of a linked pro-drug salt or the dual-acting compound, the linking moiety or the cation, respectively, is preferably a positively charged mono-, di- or tri-valent cation, an organic base or an amino acid. Preferred cations (Cat) both for the linked pro-drug in general and the dual-acting compound, in particular the complex are basic cations, even more preferably metallic cations. Preferred metallic cations include, but are not limited to Na, K, Ca, Mg, Zn,

Fe or NH_4. Amine bases and salt forming agents may also be employed, such as benzathine, hydrabamine, ethylenediamine, n-n-dibenzyl-ethylenediamine, L-arginine, choline hydroxide, N-methyl-glucamine, (Meglumine), L-Lysine, dimethylaminoethanol (Deanol), t-butylamine, diethylamine, 2-(diethylamino)-ethanol, 4-(2-hydroxyethyl)-morpholine, Thromethanine (TRIS), 4-acetamidophenol, 2-amino-2-methyl-1,3-propanediol, 2-amino-2-methyl-propanol, benzylamine, cyclohexylamine, diethanolamine, ethanolamine, imidazole, piperazine and triethanolamine.

Most preferably, the cation is Na, K or NH_4, such as Na. In one embodiment Ca is preferred.

In the case of a linked pro-drug co-crystal, the linking moiety is may also be a neutral molecule which provides hydrogen-bonding functionality.

In one embodiment, the linked pro-drugs of this invention are represented as set forth below, wherein scheme (1) and (2) represent a salt and scheme (3) represents a co-crystal:

NEPi-Xa-ARB scheme (1)

NEPi-XaYb-ARB scheme (2)

NEPi-Zc-ARB scheme (3),

wherein

X is Ca, Mg, Zn or Fe;

Y is Na, K or NH4;

Z is a neutral molecule; and

a, b and c reflect the stoichiometry of the linked pro-drug, preferably, a, b and c are a valence of 1^+, 2^+ or 3^+.

For the linked pro-drugs of schemes (1) and (2), above, preferably the NEPi is a monoprotic acid and ARB is a diprotic acid. The angiotensin receptor blocker has a charge of 0, 1 or 2 and the NEPi has a charge of 0 or 1 depending on the pH of the solution, while the overall molecule will be neutral. Ratios of ARB to NEPi will be 1:1, 1:2, 1:3, 3:1, 2:1, 1:1, preferably 1:1, 1:2 or 1:3, most preferably 1:1.

Multi-component salts, particularly with zinc and calcium have been reported in the literature, e.g., *Chem Pharm Bull*, Vol. 53, p. 654 (2005). These ions require a coordination geometry that facilitates the crystallization of multi-component systems. The metal ions have coordinating geometries governed by the atomic orbitals for each species

Valsartan comprises two acidic groupings: the carboxylic acid and the tetrazole. In one embodiment of this aspect of the present invention, the molecular structure of linked pro-drugs of valsartan and a NEPi comprise a linkage between the carboxylic acid and the linking moiety or a linkage between the tetrazole grouping and the linking moiety. In yet another embodiment, the linked pro-drug comprises a trivalent linking moiety linked to the valsartan carboxylic acid grouping, the tetrazole grouping and the NEPi grouping.

In an embodiment of this aspect of the invention, valsartan is linked to (2R,4S)-5-biphenyl-4-yl-4-(3-carboxy-propionylamino)-2-methyl-pentanoic acid ethyl ester by a calcium salt ion.

In a preferred embodiment of the present application, the angiotensin receptor antagonist and the neutral endopeptidase inhibitor are present in a molar ratio of 1:1, 1:2, 1:3, 3:1, 2:1, more preferably 1:1 in the combination as well as in the supramolecular complex. This is also true for the linked pro-drug. Moreover, in the complex, angiotensin receptor antagonist, the neutral endopeptidase inhibitor and the cation are present in a molar ratio of 1:1:1, 1:1:2, 1:1:3, more preferably 1:1:3. This applies equally to the linked pro-drug.

The combination or the dual-acting compound, in particular the complex of the present invention may contain a solvent. This is particularly preferred in the case of the dual-acting compound, in particular the complex, where the solvent may contribute to the intermolecular structure, e.g. the supramolecular interactions. Preferred solvents include water, methanol, ethanol, 2-propanol, acetone, ethyl acetate, methyl-t-butylether, acetonitrile, toluene, and methylene chloride, preferably water. If a solvent is present, one or more molecules per molecule of the active agent can be present. In this case, namely if a stoichiometric amount of the solvent is present, preferably 1, 2, 3, 4 or 5, more preferably 3, molecules of solvent, such as water, can be present per molecule of active agent. Alternatively, the solvent may be present in non-stoichiometric amounts. This means preferably any stoichiometric fraction of the solvent, such as 0.25, 0.5, 0.75, 1.25, 1.5, 1.75, 2.25, 2.5, 2.75, 3.25, 3.5, 3.75, 4.25, 4.5 and 4.75, preferably 2.5, molecules of solvent, such as water, can be present per molecule of active agent. If the dual-acting compound, in particular the complex is in the crystalline form, the solvent may be part of the molecular packing and be trapped in the crystal lattice.

Thus in a preferred embodiment of the present invention, the dual-acting compound, in particular the supramolecular complex is described by the sum formula:

[ARB(NEPi)]$Na_{1-3}.xH_2O$, wherein x is 0, 1, 2 or 3, such as 3, preferably

[ARB(NEPi)]$Na_3.xH_2O$, wherein x is 0, 1, 2 or 3, such as 3, more preferably

[valsartan ((2R,4S)-5-biphenyl-4-yl-4-(3-carboxy-propionylamino)-2-methyl-pentanoic acid ethyl ester)]$Na_3.x H_2O$, wherein x is 0, 1, 2 or 3, such as 3.

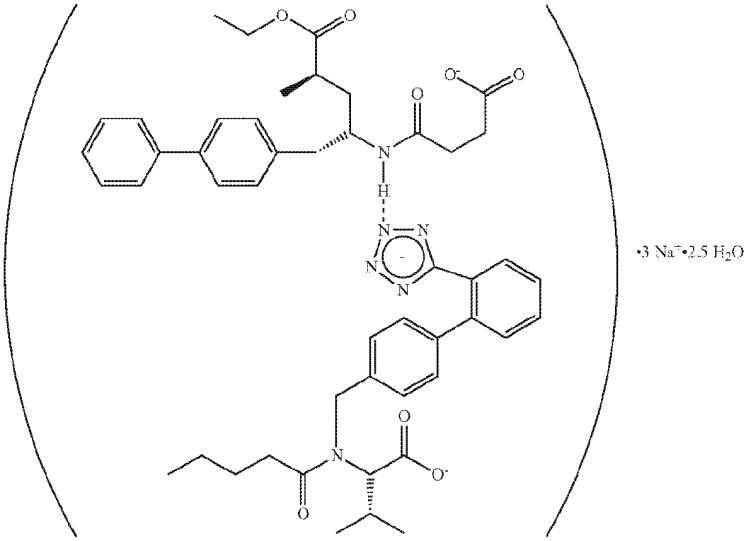
Thus in a preferred embodiment of the present invention, the dual-acting compound, in particular the supramolecular complex is described by the sum formula:

[ARB(NEPi)]$Na_{1-3}.xH_2O$, wherein x is 0 to 3, such as 2.5, preferably

[ARB(NEPi)]$Na_3.xH_2O$, wherein x is 0 to 3, such as 2.5, more preferably

[(N-valeryl-N-{[2'-(1H-tetrazole-5-yl)-biphenyl-4-yl]-methyl}-valine) (5-biphenyl-4-yl-4-(3-carboxy-priopionylamino)-2-methyl-pentanoic acid ethyl ester]$Na_3.x H_2O$, in particular [((S)—N-valeryl-N-{[2'-(1H-tetrazole-5-yl)-biphenyl-4-yl]-methyl}-valine) ((2R,4S)-5-biphenyl-4-yl-4-(3-carboxy-propionylamino)-2-methyl-pentanoic acid ethyl ester]$Na_3.x H_2O$, wherein x is 0 to 3, such as 2.5. In this most preferred example, the complex is termed trisodium [3-((1 S,3R)-1-biphenyl-4-ylmethyl-3-ethoxycarbonyl-1-butylcarbamoyl) propionate-(S)-3'-methyl-2'-(pentanoyl{2"-(tetrazol-5-ylate) biphenyl-4'-ylmethyl}amino) butyrate] hemipentahydrate.

A simplified structure of trisodium [3-((1 S,3R)-1-biphenyl-4-ylmethyl-3-ethoxycarbonyl-1-butylcarbamoyl)propionate-(S)-3'-methyl-2'-(pentanoyl{22"-(tetrazol-5-ylate)biphenyl-4'-ylmethyl}amino)butyrate] hemipentahydrate used to formally calculate the relative molecular mass, is shown below.



Valsartan comprises two acidic groupings: the carboxylic acid and the tetrazole. In one embodiment of this aspect of the present invention, the molecular structure of the dual-acting compound, in particular, the complex, of valsartan and a NEPi comprises an interaction between the carboxylic acid and the cation, such as Na, or the solvent, such as water, or a linkage between the tetrazole grouping and the cation, such as Na, or the solvent, such as water. In yet another embodiment, the dual-acting compound, in particular, the complex, comprises an interaction between the valsartan carboxylic acid grouping, the tetrazole grouping or the NEPi grouping and the cation, such as Na, or the solvent, such as water.

The combination or dual-acting compound, in particular, the complex, of the present invention is preferably in the solid form. In the solid state it can be in the crystalline, partially crystalline, amorphous, or polymorphous form, preferably in the crystalline form.

The dual-acting compound, in particular, the complex, of the present invention is distinct from a combination of an ARB and a NEPi obtained by simply physically mixing the two active agents. Thus, it can have different properties that make it particularly useful for manufacturing and therapeutic applications. The difference of the dual-acting compound, in particular, the complex, and the combination can be exemplified by the dual-acting compound of (S)—N-valeryl-N-{[2'-(1H-tetrazole-5-yl)-biphenyl-4-yl]-methyl}-valine and (2R,4S)-5-biphenyl-4-yl-4-(3-carboxy-propionylamino)-2-methyl-pentanoic acid ethyl ester which is characterized by very distinct spectral peaks and shifts that are not observed in the physical mixture.

Specifically, such a dual-acting compound is preferably characterized by an X-ray powder diffraction pattern taken with a Scintag XDS2000 powder diffractometer using Cu-Ka radiation (lamda=1.54056 A) with a Peltier-cooled Silicon detector at room temperature (25 degree C.). Scan range was from 1.5 degree to 40 degree in 2 theta with a scan rate of 3 degree/minute. The most important reflections in the X-ray diffraction diagram comprise the following interlattice plane intervals:

The preferred characterization of trisodium [3-((1S,3R)-1-biphenyl-4-ylmethyl-3-ethoxycarbonyl-1-butylcarbamoyl)propionate-(S)-3'-methyl-2'-(pentanoyl{2"-(tetrazol-5-ylate)biphenyl-4'-ylmethyl}amino)butyrate] hemipentahydrate is obtained from the interlattice plane intervals d of the ascertained X-ray diffraction diagrams, whereby, in the following, average values 2Θ in [°] are indicated (error limit of ±0.2)

4.5, 5.5, 5.6, 9.9. 12.8, 15.7, 17.0, 17.1, 17.2, 18.3, 18.5, 19.8, 21.5, 21.7, 23.2, 23.3, 24.9, 25.3, 27.4, 27.9, 28.0, 30.2.

or with an error limit of ±0.1:

4.45, 5.52, 5.57, 9.94, 12.82, 15.66, 17.01, 17.12, 17.2, 18.32, 18.46, 19.76, 21.53, 21.72, 23.17, 23.27, 24.88, 25.3, 27.4, 27.88, 28.04, 30.2.

The most intensive reflections in the X-ray diffraction pattern show the following interlattice plane intervals:

2Θ in [°]: 0.4.5, 5.6, 12.8, 17.0, 17.2, 19.8, 21.5, 27.4, in particular 4.45, 5.57, 17.01, 17.2, 19.76, 21, 27.4.

A preferred method of checking the above-indicated average values of the interlattice plane intervals and intensities measured by experimentation from X-ray diffraction, for a given substance, consists in calculating these intervals and their intensities from the comprehensive single crystal structure determination. This structure determination yields cell constants and atom positions, which enable the X-ray diffraction diagram corresponding to the solid to be calculated by means of computer-aided calculation methods. The program used is Powder Pattern within the application software Materials Studio (Accelrys). A comparison of these data, namely the interlattice plane intervals and intensities of the most important lines of trisodium [3-((1 S,3R)-1-biphenyl-4-ylmethyl-3-ethoxycarbonyl-1-butylcarbamoyl)propionate-(S)-3'-methyl-2'-(pentanoyl{22"-(tetrazol-5-ylate)biphenyl-4'-ylmethyl}amino)butyrate] hemipentahydrate, obtained from measurements and from calculating the single crystal data, is illustrated in the table below.

TABLE

measured		calculated		measured		calculated	
2θ in [°]	Intensity	2θ in [°]	Intensity	2θ in [°]	Intensity	2θ in [°]	Intensity
4.45	very strong	4.15	very strong	19.76	strong	19.6	very weak
5.52	Strong	5	strong	21.53	weak	19.8	very weak
5.57	strong	6.5	strong	21.72	very weak	21.4	very weak
9.94	very weak	9.75	weak	23.17	weak	23.1	very weak
12.82	very strong	12.6	weak	23.27	weak	23.15	very weak
15.66	very weak	15.05	strong	24.88	very weak		very weak
17.01	weak	16.9	very strong	25.3	weak	25.3	very weak
17.12	strong	17.1	strong	27.4	weak	27.3	very weak
17.2	weak	17.15	weak	27.88	very weak	27.9	very weak
18.32	weak	18.25	very weak	28.04	weak		
18.46	weak	18.3	weak	30.2	weak		

Relative intensity between 100% to 50% is referred to as very strong, 50% to 10% as strong, 10% to 5% as weak, and below 5% as very weak

The invention relates to trisodium [3-((1S,3R)-1-biphenyl-4-ylmethyl-3-ethoxycarbonyl-1-butylcarbamoyl)propionate-(S)-3'-methyl-2'-(pentanoyl{22"-(tetrazol-5-ylate)biphenyl-4'-ylmethyl}amino)butyrate] hemipentahydrate, a crystalline solid which is characterized by the data and parameters obtained from single crystal X-ray analysis and X-ray powder patterns. An in-depth discussion of the theory of the methods of single crystal X-ray diffraction and the definition of the evaluated crystal data and the parameters may be found in Stout & Jensen, X-Ray Structure Determination; A Practical Guide, Mac Millian Co., New York, N.Y. (1968) chapter 3.

Crystal data	
sum formula	$C_{48}H_{55}N_6O_8Na_3 \cdot 2.5H_2O$
molecular mass	957.99
crystal colour	colourless
crystal shape	tabular: hexagonal
crystal system	monoclinic
space group	$P2_1$
Cell parameters	a = 20.344 Å b = 42.018 Å c = 20.374 Å α = 90° β = 119.29° γ = 90°
volume of unit cell	15190.03 Å^3
Z (the number of asymmetric units in the unit cell)	2
calculated density	1.26845 g/cm3
Single crystal X-ray measurement data	
diffractometer	Nonius KappaCCD
X-ray generator	Nonius FR571 X-ray generator with a copper rotating anode
temperature	270 K and 150 K

Notes:
Two data sets on two suitable single crystals were collected at two different temperatures to assure no phase change during cooling.
None of the hydrogen atoms on the water or amine nitrogen atoms were observed in the Fourier maps so they were not included in the refinement.

Computer Program Used to Solve the Structure SHELXD (Sheldrick, Göttingen)

In three dimensions, the unit cell is defined by three edge lengths a, b, and c, and three interaxial angles α, β, und γ. In this way, the volume of the unit cell V_c is determined. A differentiated description of these crystal parameters is illustrated in chapter 3 of Stout & Jensen (see above). The details for trisodium [3-((1S,3R)-1-biphenyl-4-ylmethyl-3-ethoxycarbonyl-1-butylcarbamoyl)propionate-(S)-3'-methyl-2'-(pentanoyl{2"-(tetrazol-5-ylate)biphenyl-4'-ylmethyl}amino)butyrate] hemipentahydrate from the single crystal measurements, especially the atom coordinates, the isotropic thermal parameters, the coordinates of the hydrogen atoms as well as the corresponding isotropic thermal parameters, show that a monoclinic unit cell exists, its cell content of twelve formula units of $C_{48}H_{55}N_6O_8Na_3.2.5\ H_2O$ occurring as a result of two asymmetric units on two-fold positions.

The acentric space group $P2_1$ determined from the single crystal X-ray structure is a common space group for enantiomorphically pure molecules. In this space group there are two general positions which means that for twelve formula units in the unit cell there must be 18 sodium ions and 15 waters in the asymmetric unit.

A pictorial representation of the unit cell of the supramolecular complex of trisodium [3-((1 S,3R)-1-biphenyl-4-ylmethyl-3-ethoxycarbonyl-1-butylcarbamoyl) propionate-(S)-3'-methyl-2'-(pentanoyl{2"-(tetrazol-5-ylate) biphenyl-4'-ylmethyl}amino)butyrate] hemipentahydrate comprising two asymmetric units is shown in FIG. **1**.

Based on the single crystal structure solution, the asymmetric unit of the trisodium [3-((1 S,3R)-1-biphenyl-4-ylmethyl-3-ethoxycarbonyl-1-butylcarbamoyl) propionate-(S)-3'-methyl-2'-(pentanoyl{2"-(tetrazol-5-ylate) biphenyl-4'-ylmethyl}amino)butyrate] hemipentahydrate supramolecule comprises six each of ARB and NEPi moieties, 18 sodium atoms, and 15 water molecules. Trisodium [3-((1 S,3R)-1-biphenyl-4-ylmethyl-3-ethoxycarbonyl-1-utylcarbamoyl)propionate-(S)-3'-methyl-2'-(pentanoyl{2"-(tetrazol-5-ylate) biphenyl-4'-ylmethyl}amino)butyrate] hemipentahydrate may be considered a sodium supramolecular complex, coordinated by oxygen ligands. These oxygens come from twelve carboxylate groups and eighteen carbonyl groups of the above moieties, and from 13 of the 15 water molecules. The crystal is an infinite 3-dimensional network of these sodium complexes.

Such a compound may also be characterized by an infrared absorption spectrum obtained using Attenuated Total Reflection Fourier Transform Infrared (ATR-FTIR) spectrometer (Nicolet Magna-IR 560) showing the following significant bands, expressed in reciprocal wave numbers (cm^{-1}):

2956 (w), 1711 (st), 1637 (st), 1597 (st), 1488 (w), 1459 (m), 1401 (st), 1357 (w), 1295 (m), 1266 (m), 1176 (w), 1085 (m), 1010 (w), 942 (w), 907 (w), 862 (w), 763 (st), 742 (m), 698 (m), 533 (st). Characteristic to the complex are in particular the following peaks 1711 (st), 1637 (st), 1597 (st) and 1401 (st). The error margin for all absorption bands of ATR-IR is ±2 cm^{-1}. The intensities of the absorption bands are indicated as follows: (w)=weak; (m)=medium; and (st) =strong intensity.

Such a compound may also be characterized by a Raman spectrum measured by dispersive Raman spectrometer with 785 nm laser excitation source (Kaiser Optical Systems, Inc.) showing the following significant bands expressed in reciprocal wave numbers (cm^{-1}):

3061 (m), 2930 (m, broad), 1612 (st), 1523 (m), 1461 (w), 1427 (w), 1287 (st), 1195 (w), 1108 (w), 11053 (w), 1041 (w), 1011 (w), 997 (m), 866 (w), 850 (w), 822 (w), 808 (w), 735 (w), 715 (w), 669 (w), 643 (w), 631 (w), 618 (w), 602 (w), 557 (w), 522 (w), 453 (w), 410 (w), 328 (w).

The error margin for all Raman bands is ±2 cm^{-1}. The intensities of the absorption bands are indicated as follows: (w)=weak; (m)=medium; and (st)=strong intensity.

Such a compound may also be characterized by distinct melting properties measured by differential scanning calorimetry (DSC). Using Q1000 (TA Instruments) instrument, the melting onset temperature and the peak maximum temperature for such a complex are observed at 139° C. and 145° C., respectively. The heating rate is 10 K/min.

The second embodiment of the present invention is directed to pharmaceutical compositions comprising a combination, a linked pro-drug or a dual-acting compound, in particular the complex as described herein and at least one pharmaceutically acceptable additive. The details regarding the combination and the complex, including the ARB and the NEPi, are as described above with regard to the first embodiment of the invention.

The pharmaceutical compositions according to the invention can be prepared in a manner known per se and are those suitable for enteral, such as oral or rectal, and parenteral administration to mammals (warm-blooded animals), including man, comprising a therapeutically effective amount of the combination or dual-acting compound, in particular the complex, alone or in combination with at least one pharmaceutically acceptable carrier, especially suitable for enteral or parenteral application. Typical oral formulations include tablets, capsules, syrups, elixirs and suspensions. Typical injectable formulations include solutions and suspensions.

Pharmaceutically acceptable additives suitable for use in the present invention include, without limitation and provided they are chemically inert so that they do not adversely affect the combination or the dual-acting compound, in particular the complex of the present invention, diluents or fillers, disintegrants, glidants, lubricants, binders, colorants and combinations thereof. The amount of each additive in a solid dosage formulation may vary within ranges conventional in the art. Typical pharmaceutically acceptable carriers for use in the formulations described above are exemplified by: sugars, such as lactose, sucrose, mannitol and sorbitol; starches, such as cornstarch, tapioca starch and potato starch; cellulose and derivatives, such as sodium carboxymethyl cellulose, ethyl cellulose and methyl cellulose; calcium phosphates, such as dicalcium phosphate and tricalcium phosphate; sodium sulfate; calcium sulfate; polyvinylpyrrolidone; polyvinyl alcohol; stearic acid; alkaline earth metal stearates, such as magnesium stearate and calcium stearate; stearic acid; vegetable oils, such as peanut oil, cottonseed oil, sesame oil, olive oil and corn oil; non-ionic, cationic and anionic surfactants; ethylene glycol polymers; β-cyclodextrin; fatty alcohols; and hydrolyzed cereal solids, as well as other non-toxic compatible fillers, binders, disintegrants, buffers, preservatives, antioxidants, lubricants, flavoring agents and the like commonly used in pharmaceutical formulations.

Pharmaceutical preparations for enteral or parenteral administration are, e.g., in unit dose forms, such as coated tablets, tablets, capsules or suppositories and also ampoules. These are prepared in a manner which is known per se, e.g., using conventional mixing, granulation, coating, solubilizing or lyophilizing processes. Thus, pharmaceutical compositions for oral use can be obtained by combining the linked pro-drug, combination or dual-acting compound, in particular the complex with solid excipients, if desired, granulating a mixture which has been obtained, and, if required or necessary, processing the mixture or granulate into tablets or coated tablet cores after having added suitable auxiliary substances.

The dosage of the active compounds in the combination or dual-acting compound, in particular the complex can depend on a variety of factors, such as mode of administration, homeothermic species, age and/or individual condition. The projected efficacy in animal disease models ranges from about 0.1 mg/kg/day to about 1000 mg/kg/day given orally, and the projected dose for human treatment ranges from about 0.1 mg/day to about 2000 mg/day. Preferred ranges are from about 40 mg/day to about 960 mg/day of the linked pro-drug, preferably about 80 mg/day to about 640 mg/day. The ARB component is administered in a dosage of from about 40 mg/day to about 320 mg/day and the NEPi component is administered in a dosage of from about 40 mg/day to about 320 mg/day. More specifically, the dosages of ARB/NEPi, respectively, include 40 mg/40 mg, 80 mg/80 mg, 160 mg/160 mg, 320 mg/320 mg, 40 mg/80 mg, 80 mg/160 mg, 160 mg/320 mg, 320 mg/640 mg, 80 mg/40 mg, 160 mg/80 mg and 320 mg/160 mg, respectively. These dosages are "therapeutically effective amounts". Preferred dosages for the linked pro-drug, combination or dual-acting compound, in particular the complex of the pharmaceutical composition according to the present invention are therapeutically effective dosages.

The pharmaceutical compositions may contain in addition another therapeutic agent, e.g., each at an effective therapeutic dose as reported in the art. Such therapeutic agents include:

a) antidiabetic agents such as insulin, insulin derivatives and mimetics; insulin secretagogues such as the sulfonylureas, e.g., Glipizide, glyburide and Amaryl; insulinotropic sulfonylurea receptor ligands such as meglitinides, e.g., nateglinide and repaglinide; peroxisome proliferator-activated receptor (PPAR) ligands; protein tyrosine phosphatase-1B (PTP-1B) inhibitors such as PTP-112; GSK3 (glycogen synthase kinase-3) inhibitors such as SB-517955, SB-4195052, SB-216763, NN-57-05441 and NN-57-05445; RXR ligands such as GW-0791 and AGN-194204; sodium-dependent glucose cotransporter inhibitors such as T-1095; glycogen phosphorylase A inhibitors such as BAY R3401; biguanides such as met-formin; alpha-glucosidase inhibitors such as acarbose; GLP-1 (glucagon like peptide-1), GLP-1 analogs such as Exendin-4 and GLP-1 mimetics; and DPPIV (dipeptidyl peptidase IV) inhibitors such as LAF237;

b) hypolipidemic agents such as 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, e.g., lovastatin, pitavastatin, simvastatin, pravastatin, cerivastatin, mevastatin, velostatin, fluvastatin, dalvastatin, atorvastatin, rosuvastatin and rivastatin; squalene synthase inhibitors; FXR (farnesoid X receptor) and LXR (liver X receptor) ligands; cholestyramine; fibrates; nicotinic acid and aspirin;

c) anti-obesity agents such as orlistat; and

d) anti-hypertensive agents, e.g., loop diuretics such as ethacrynic acid, furosemide and torsemide; angiotensin converting enzyme (ACE) inhibitors such as benazepril, captopril, enalapril, fosinopril, lisinopril, moexipril, perinodopril, quinapril, ramipril and trandolapril; inhibitors of the Na—K-ATPase membrane pump such as digoxin; ACE/NEP inhibitors such as omapatrilat, sampatrilat and fasidotril; 3-adrenergic receptor blockers such as acebutolol, atenolol, betaxolol, bisoprolol, metoprolol, nadolol, propranolol, sotalol and timolol; inotropic agents such as digoxin, dobutamine and milrinone; calcium channel blockers such as amlodipine, bepridil, diltiazem, felodipine,

nicardipine, nimodipine, nifedipine, nisoldipine and verapamil; aldosterone receptor antagonists; and aldosterone synthase inhibitors. Most preferred combination partners are diuretics, such as hydrochlorothiazide, and/or calcium channel blockers, such as amlodipine or a salt thereof.

Other specific anti-diabetic compounds are described by Patel Mona in *Expert Opin Investig Drugs*, 2003, 12(4), 623-633, in the FIGS. 1 to 7, which are herein incorporated by reference.

A compound of the present invention may be administered either simultaneously, before or after the other active ingredient, either separately by the same or different route of administration or together in the same pharmaceutical formulation.

The structure of the therapeutic agents identified by code numbers, generic or trade names may be taken from the actual edition of the standard compendium "The Merck Index" or from databases, e.g., Patents International (e.g. IMS World Publications). The corresponding content thereof is hereby incorporated by reference.

Accordingly, the present invention provides pharmaceutical compositions in addition a therapeutically effective amount of another therapeutic agent, preferably selected from antidiabetics, hypolipidemic agents, anti-obesity agents or anti-hypertensive agents, most preferably from antidiabetics, anti-hypertensive agents or hypolipidemic agents as described above.

The person skilled in the pertinent art is fully enabled to select a relevant test model to prove the efficacy of a combination of the present invention in the hereinbefore and hereinafter indicated therapeutic indications.

Representative studies are carried out with trisodium [3-((1 S,3R)-1-biphenyl-4-ylmethyl-3-ethoxycarbonyl-1-butylcarbamoyl)propionate-(S)-3'-methyl-2'-(pentanoyl{2"-(tetrazol-5-ylate)biphenyl-4'-ylmethyl}amino)butyrate] hemipentahydrate, e.g. applying the following methodology:

The antihypertensive and neutral endopeptidase 24.11 (NEP)-inhibitory activities of trisodium [3-((1 S,3R)-1-biphenyl-4-ylmethyl-3-ethoxycarbonyl-1-butylcarbamoyl) propionate-(S)-3'-methyl-2'-(pentanoyl{2"-(tetrazol-5-ylate)biphenyl-4'-ylmethyl}amino) butyrate] hemipentahydrate is assessed in conscious rats. The blood pressure-lowering effect is evaluated in double-transgenic rats (dTGRs) that overexpress both human renin and its substrate, human angiotensinogen (Bohlender, et al, High human renin hypertension in transgenic rats. Hypertension; 29(1 Pt 2):428-34, 1997). Consequently, these animals exhibit an angiotensin II-dependent hypertension. The NEP-inhibitory effect of trisodium [3-((1 S,3R)-1-biphenyl-4-ylmethyl-3-ethoxycarbonyl-1-butylcarbamoyl) propionate-(S)-3'-methyl-2'-(pentanoyl{2"-(tetrazol-5-ylate)biphenyl-4'-ylmethyl}amino)butyrate] hemipentahydrate is determined in conscious Sprague-Dawley rats infused with exogenous atrial natriuretic peptide (ANP). Potentiation of plasma ANP levels is used as an index of NEP inhibition in vivo. In both models, trisodium [3-((1S, 3R)-1-biphenyl-4-ylmethyl-3-ethoxycarbonyl-1-butylcarbamoyl)propionate-(S)-3'-methyl-2'-(pentanoyl{22"-(tetrazol-5-ylate)biphenyl-4'-ylmethyl}amino)butyrate] hemipentahydrate is administered orally as a powder in gelatin mini capsules. The results are summarized below.

Trisodium [3-((1 S,3R)-1-biphenyl-4-ylmethyl-3-ethoxycarbonyl-1-butylcarbamoyl)propionate-(S)-3'-methyl-2'-(pentanoyl{2"-(tetrazol-5-ylate) biphenyl-4'-ylmethyl}amino)butyrate] hemipentahydrate exhibits a dose-dependent and long-lasting antihypertensive effect after oral administration in conscious dTGRs, a rat model of fulminant hypertension.

Oral administration of trisodium [3-((1S,3R)-1-biphenyl-4-ylmethyl-3-ethoxycarbonyl-1-butylcarbamoyl)propionate-(S)-3'-methyl-2'-(pentanoyl{2"-(tetrazol-5-ylate) biphenyl-4'-ylmethyl}amino)butyrate] hemipentahydrate rapidly and dose-dependently inhibits NEP with a long duration of action, as reflected by its potentiation of plasma ANP immunoreactivity (ANPir) in conscious Sprague-Dawley rats infused with exogenous ANP.

Antihypertensive Effect In Vivo

The dTGRs are instrumented with radiotelemetry transmitters for continuous measurement of arterial blood pressure and heart rate. Animals are randomly assigned to vehicle (empty capsule) or treatment (at 2, 6, 20 or 60 mg/kg, p.o.) groups. Baseline 24-hr mean arterial pressure (MAP) is approximately 170-180 mmHg in all groups. Trisodium [3-((1S,3R)-1-biphenyl-4-ylmethyl-3-ethoxycarbonyl-1-butylcarbamoyl)propionate-(S)-3'-methyl-2'-(pentanoyl{2"-(tetrazol-5-ylate)biphenyl-4'-ylmethyl}amino) butyrate] hemipentahydrate dose-dependently reduces MAP. The values obtained from the treatment groups are dose-dependent, and the results from the three highest doses are significantly different from the vehicle controls

Inhibition of NEP In Vivo

The extent and duration of trisodium [3-((1S,3R)-1-biphenyl-4-ylmethyl-3-ethoxycarbonyl-1-butylcarbamoyl) propionate-(S)-3'-methyl-2'-(pentanoyl{22"-(tetrazol-5-ylate)biphenyl-4'-ylmethyl}amino)butyrate] hemipentahydrate for NEP inhibition in vivo is assessed with methodologies as described previously (Trapani, et al, CGS 35601 and its orally active prodrug CGS 37808 as triple inhibitors of endothelin-converting enzyme-1, neutral endopeptidase 24.11, and angiotensin-converting enzyme. J Cardiovasc Pharmacol; 44(Suppl 1):S211-5, 2004). Rat ANP(1-28) is infused intravenously at a rate of 450 ng/kg/min in conscious, chronically cannulated, male Sprague-Dawley rats. After one hour of infusion, rats are randomly assigned to one of six groups: untreated control, vehicle (empty capsule) control, or one of four doses of drug (2, 6, 20, or 60 mg/kg, p.o.). ANP infusion is continued for an additional eight hours. Blood samples are collected for measuring plasma ANPir by a commercial enzyme immunoassay kit at −60 min (i.e., before initiating ANP infusion), −30 min (after 30 min of ANP infusion), 0 min ("baseline"; after 60 min of ANP infusion but before dosing with drug or its vehicle), and at 0.25, 0.5, 1, 2, 3, 4, 5, 6, 7, and 8 hr post-dosing.

Before ANP infusion, ANPir is low (0.9-1.4 ng/ml) and similar in all six groups. ANP infusion rapidly (by 30 min) elevates ANPir to ~10 ng/ml. This ANPir level is sustained for the duration of the experiment in the untreated and vehicle control groups. In contrast, trisodium [3-((1 S,3R)-1-biphenyl-4-ylmethyl-3-ethoxycarbonyl-1-butylcarbamoyl)propionate-(S)-3'-methyl-2'-(pentanoyl{2"-(tetrazol-5-ylate)biphenyl-4'-ylmethyl}amino)butyrate] hemipentahydrate rapidly (within 15 min) and dose-dependently augments ANPir. In summary, orally administered LCZ696 rapidly and dose-dependently inhibited NEP with a long duration of action as reflected by the potentiation of plasma ANPir.

The available results indicate an unexpected therapeutic effect of a compound according to the invention.

In a third aspect, the present invention is directed to a method of making a linked pro-drug of an ARB or a

pharmaceutically acceptable salt thereof and a NEPi or a pharmaceutically acceptable salt thereof comprising the steps of:

(a) adding an inorganic salt forming agent to a solvent to form a linked pro-drug salt forming solution;

(b) adding the salt forming solution to a mixture of an ARB and a NEPi such that the ARB and NEPi form a linked pro-drug; and

(c) isolating the linked pro-drug.

Preferably, the components are added in an equivalent amount.

The inorganic salt forming agent includes, but is not limited to, calcium hydroxide, zinc hydroxide, calcium methoxide, calcium acetate, calcium hydrogen carbonate, calcium formate, magnesium hydroxide, magnesium acetate, magnesium formate and magnesium hydrogen carbonate, sodium hydroxide, sodium methoxide, sodium acetate, sodium formate. The inorganic salt forming agent releases the linking moiety into the solvent such that when an ARB and a NEPi are present a linked pro-drug is formed.

Solvents included in the scope of the present invention include, but are not limited to, solvents in which the ARB, NEPi and inorganic salt forming agent preferably exhibit a lower solubility that allows the linked pro-drug to crystallize. Such solvents may comprise, but are not limited to, water, methanol, ethanol, 2-propanol, ethyl acetate, methyl-t-butylether, acetonitrile, toluene, and methylene chloride and mixtures of such solvents.

The inorganic salt forming agent and the solvent when combined should have a pH which promotes linked pro-drug formation. The pH may be between about 2 and about 6, preferably between about 3 and about 5, most preferably between 3.9 and 4.7.

The linked pro-drug is isolated by crystallization and chromatography. Specific types of chromatography include, e.g., ligand specific resin chromatography, reverse phase resin chromatography and ion-exchange resin chromatography.

A specific example comprises contacting a divalent salt of one component with a monovalent salt of the other component of the linked pro-drug. Specifically the mixed salt of valsartan and a mono-basic NEPi are synthesized by contacting the calcium salt of valsartan with the sodium salt of the NEPi component. Isolation of the desired mixed salt is carried out by selective crystallization or chromatography using ligand specific resins, reverse phase resins or ion-exchange resins. Similarly this process can be conducted with a monovalent salt of both components, such as the sodium salt of both components.

In another embodiment of this aspect of the invention, a co-crystal of the linked pro-drug is obtained. In a method of making a linked pro-drug co-crystal the inorganic salt forming agent is replaced with a neutral molecule which provides hydrogen binding properties. The solvent may be part of the molecular packing and be trapped in the crystal lattice.

In a preferred embodiment of the third aspect, the present invention is directed to a method of preparing a dual-acting compound comprising

(a) an angiotensin receptor antagonist;

(b) a neutral endopeptidase inhibitor (NEPi); and optionally

(c) a pharmaceutically acceptable cation;

said method comprising the steps of:

(i) dissolving an angiotensin receptor antagonist and a neutral endopeptidase inhibitor (NEPi) in a suitable solvent;

(ii) dissolving a basic compound of Cat in a suitable solvent, wherein Cat is a cation;

(iii) combining the solutions obtained in steps (i) and (ii);

(iv) precipitation of the solid, and drying same to obtain the dual-acting compound; or alternatively obtaining the dual-acting compound by exchanging the solvent(s) employed in steps (i) and (ii) by

(iva) evaporating the resulting solution to dryness;

(va) re-dissolving the solid in a suitable solvent;

(via) precipitation of the solid and drying same to obtain the dual-acting compound.

The details regarding the complex, including the ARB, the NEPi and the cation, are as described above with regard to the first embodiment of the invention.

Preferably, in step (i) the ARB and the NEPi are added in an equivalent molar amount. Both the ARB and the NEPi are preferably used in the free form. The solvent used in step (i) may be any solvent that allows dissolution of both the ARB and the NEPi. Preferred solvents include those mentioned above, namely water, methanol, ethanol, 2-propanol, acetone, ethyl acetate, isopropyl acetate, methyl-t-butylether, acetonitrile, toluene, DMF, NMF and methylene chloride and mixtures of such solvents, such as ethanol-water, methanol-water, 2-propanol-water, acetonitrile-water, acetone-water, 2-propanol-toluene, ethyl acetate-heptane, isopropyl acetate-acetone, methyl-t-butyl ether-heptane, methyl-t-butyl ether-ethanol, ethanol-heptane, acetone-ethyl acetate, acetone-cyclohexane, toluene-heptane, more preferably acetone.

Preferably, in step (ii) the basic compound of Cat is a compound capable of forming a salt with the acidic functionalities of the ARB and the NEPi. Examples include those mentioned above, such as calcium hydroxide, zinc hydroxide, calcium methoxide, calcium ethoxide, calcium acetate, calcium hydrogen carbonate, calcium formate, magnesium hydroxide, magnesium acetate, magnesium formate, magnesium hydrogen carbonate, sodium hydroxide, sodium carbonate, sodium hydrogen carbonate, sodium methoxide, sodium ethoxide, sodium acetate, sodium formate, potassium hydroxide, potassium carbonate, potassium hydrogen carbonate, potassium methoxide, potassium ethoxide, potassium acetate, potassium formate, ammonium hydroxide, ammonium methoxide, ammonium ethoxide, and ammonium carbonate. Perchlorates may also be used. Amine bases or salt forming agents such as those mentioned above may also be used, in particular benzathine, L-arginine, cholin, ethylene diamine, L-lysine or piperazine. Typically an inorganic base is employed with Cat as specified herein. More preferably, the basic compound is $(Cat)OH$, $(Cat)_2CO_3$, $(Cat)HCO_3$, still more preferably Cat(OH), such as NaOH. The basic compound is employed in an amount of at least 3 equivalents relative to either the ARB or the NEPi, preferably it is employed in stoichiometric amount to obtain the dual-acting compound, in particular the complex with three cations. The solvent used in step (ii) may be any solvent or mixtures of solvents that allow dissolution of Cat(OH). Preferred solvents include water, methanol, ethanol, 2-propanol, acetone, ethyl acetate, isopropyl acetate, methyl-t-butylether, acetonitrile, toluene, and methylene chloride and mixtures of such solvents, more preferably water.

In step (iii) the solutions obtained in steps (i) and (ii) are combined. This can take place by adding the solution obtained in step (i) to the solution obtained in step (ii) or vice versa, preferably, the solution obtained in step (ii) to the solution obtained in step (i).

According to the first alternative, once combined and preferably mixed, the dual-acting compound, in particular

the complex precipitates in step (iv). This mixing and precipitation is typically effected by stirring the solutions for an appropriate amount of time such as 20 min to 6 h, preferably 30 min to 3 h, more preferably 2 h, at room temperature. It is advantageous to add seeds of the dual acting compound. This method facilitates precipitation.

In step (iv) according to this first alternative, a co-solvent is typically added. The co-solvent employed is a solvent in which the ARB and the NEPi in the complexed form exhibit a lower solubility that allows the compound to precipitate. Distillation, either continuous or stepwise, with replacement by this co-solvent results in a mixture predominantly of the co-solvent. Preferred solvents include ethanol, 2-propanol, acetone, ethyl acetate, isopropyl acetate, methyl-t-butylether, acetonitrile, toluene, and methylene chloride and mixtures of such solvents, more preferably isopropyl acetate. Preferably, a minimum amount of solvent is employed to facilitate precipitation. The solid is collected, e.g. by filtration, and is dried to obtain the dual-acting compound, in particular the complex in accordance with the present invention. The drying step can be performed at room temperature or elevated temperature such as 30 to 60° C., preferably 30 to 40° C. Reduced pressure can be employed to facilitate removal of the solvent, preferably, drying is effected at ambient pressure or reduced pressure of e.g. 10 to 30 bar, such as 20 bar.

According to a second alternative, once combined and preferably mixed, the dual-acting compound, in particular the complex the mixture preferably forms a clear solution. This mixing is typically effected by stirring the solutions for an appropriate amount of time such as 20 min to 6 h, preferably 30 min to 3 h, more preferably 1 h, at room temperature. If necessary, the temperature may be raised so as to ensure a clear solution.

The obtained mixture is then further treated by solvent exchange to obtain the dual-acting compound, in particular the complex.

In step (iva) according to this second alternative, the solution is preferably evaporated to dryness at elevated temperatures such as >room temperature to 50° C., more preferably 30 to 40° C.

Preferably, in step (va) the solvent or solvent mixture employed is a solvent in which the ARB and the NEPi in the complexed form exhibit a lower solubility that allows the dual-acting compound, in particular the complex to precipitate. Preferred solvents include the ones mentioned above for step (i), such as water, ethanol, 2-propanol, acetone ethyl acetate, isopropyl acetate, methyl-t-butylether, acetonitrile, toluene, and methylene chloride and mixtures of such solvents, more preferably isopropyl acetate. Preferably, a minimum amount of solvent or solvent mixture is employed to facilitate precipitation.

In step (via) precipitation can take place at room temperature. It can be effected by leaving the mixture standing or by agitating the mixture, preferably by agitating it. This is preferably effected by stirring and/or sonication. After precipitation, the solid is collected, e.g. by filtration, and is dried to obtain the compound in accordance with the present invention. The drying step can be performed at room temperature or elevated temperature such as 30 to 60° C., preferably room temperature. Reduced pressure can be employed to facilitate removal of the solvent, preferably, drying is effected at ambient pressure.

In a fourth aspect, this invention is directed to a method of treating or preventing a disease or condition, such as hypertension, heart failure (acute and chronic) congestive heart failure, left ventricular dysfunction and hypertrophic cardiomyopathy, diabetic cardiac myopathy, supraventricular and ventricular arrhythmias, atrial fibrillation, atrial flutter, detrimental vascular remodeling, myocardial infarction and its sequelae, atherosclerosis, angina (unstable or stable), renal insufficiency (diabetic and non-diabetic), heart failure, angina pectoris, diabetes, secondary aldosteronism, primary and secondary pulmonary hypertension, renal failure conditions, such as diabetic nephropathy, glomerulonephritis, scleroderma, glomerular sclerosis, proteinuria of primary renal disease, and also renal vascular hypertension, diabetic retinopathy, other vascular disorders, such as migraine, peripheral vascular disease, Raynaud's disease, luminal hyperplasia, cognitive dysfunction (such as Alzheimer's), glaucoma and stroke comprising administering the afore-mentioned combination, linked pro-drug or the dual-acting compound, in particular the complex to a subject in need of such treatment.

The combination, linked pro-drug or the dual-acting compound, in particular the complex of the first embodiment may be administered alone or in the form of a pharmaceutical composition according to the second embodiment. Information regarding dosing, i.e., the therapeutically effective amount, etc., is the same regardless of how the combination, linked pro-drug or he dual-acting compound, in particular the complex is administered.

The combination, linked pro-drug or the dual-acting compound, in particular the complex is beneficial over a combination of ARBs or neutral endopeptidase inhibitors alone or other ARB/NEPi combinations with regard to use as first line therapy, ease of formulation and ease of manufacture.

Specific embodiments of the invention will now be demonstrated by reference to the following examples. It should be understood that these examples are disclosed solely by way of illustrating the invention and should not be taken in any way to limit the scope of the present invention.

Example 1

Preparation of [valsartan ((2R,4S)-5-biphenyl-4-yl-4-(3-carboxy-propionylamino)-2-methyl-pentanoic acid ethyl ester)]Na_3.2.5 H_2O

The dual-acting compound of valsartan and (2R,4S)-5-biphenyl-4-yl-4-(3-carboxy-propionylamino)-2-methyl-pentanoic acid ethyl ester is prepared by dissolving 0.42 g of (2R,4S)-5-biphenyl-4-yl-4-(3-carboxy-propionylamino)-2-methyl-pentanoic acid ethyl ester free acid (~95% purity) and 0.41 g of valsartan free acid in 40 ml acetone. Separately, 0.111 g of NaOH are dissolved in 7 ml H_2O. The two solutions are combined and stirred at room temperature for 1 hour and a clear solution was obtained. The solution is evaporated at 35° C. to yield a glassy solid. The glassy solid residue is then charged with 40 ml acetone and the resulting mixture is stirred and sonicated until precipitation occurred (~5 minutes). The precipitate was filtered and the solid is dried at room temperature in open air for 2 days until a constant mass of the crystalline solid is obtained.

Characterization by various methods could confirm the presence of both valsartan and (2R,4S)-5-biphenyl-4-yl-4-(3-carboxy-propionylamino)-2-methyl-pentanoic acid ethyl ester and complex formation in contrast to a simple physical mixture. Significant spectral peaks for the complex are observed e.g. in the XRPD, IR, and Raman spectroscopy which are not present for the physical mixture. See below for details on the characterization.

Example 2

Alternative Preparation of [valsartan ((2R,4S)-5-biphenyl-4-yl-4-(3-carboxy-propionylamino)-2-methyl-pentanoic acid ethyl ester)]Na_3.2.5 H_2O

The dual acting compound of valsartan and (2R,4S)-5-biphenyl-4-yl-4-(3-carboxy-propionylamino)-2-methyl-pentanoic acid ethyl ester is prepared by dissolving 22.96 mmol of (2R,4S)-5-biphenyl-4-yl-4-(3-carboxy-propionylamino)-2-methyl-pentanoic acid ethyl ester free acid (~95% purity) and valsartan (10.00 g; 22.96 mmol) in acetone (300 mL). The suspension is stirred at room temperature for 15 min to obtain a clear solution. A solution of NaOH (2.76 g; 68.90 mmol) in water (8 mL) water is then added to this solution over a period of 10 min. Solids start to precipitate in 10 min. Alternatively, precipitation can be induced by seeding. The suspension is stirred at 20-25° C. for 2 h. This suspension is concentrated at 15-30° C. under reduced pressure (180-250 mbar) to a batch volume of ~150 mL. Isopropyl acetate (150 mL) is then added to the batch and the suspension is concentrated again at 15-30° C. under reduced pressure (180-250 mbar) to a batch volume of ~150 mL. This operation (addition of 150 mL of isopropyl acetate to the batch and concentration) is repeated once again. The suspension is stirred at 20-25° C. for 1 h. The solids are collected by filtration under nitrogen over a Büchner funnel, washed with isopropyl acetate (20 mL), and dried at 35° C. under reduced pressure (20 mbar) to afford the compound.

Characterization revealed the same product as in Example 1.

Example 3

Alternative Preparation of [valsartan ((2R,4S)-5-biphenyl-4-yl-4-(3-carboxy-propionylamino)-2-methyl-pentanoic acid ethyl ester)]Na_3.2.5 H_2O Using Seeding

A reactor is charged with 2.00 kg (2,323 mmol) of AHU377 calcium salt and 20 L of isopropyl acetate. The suspension is stirred at 23±3° C., and 4.56 L of 2 N HCl was added. The mixture is stirred at 23±3° C. for 15 min to obtain a clear two-phase solution. The organic layer is separated and washed with 3×4.00 L of water. The organic layer is concentrated at 30-100 mbar and 22±5° C. to ~3.5 L (3.47 kg) of AHU377 free acid isopropyl acetate solution as a colorless solution.

To the above reactor containing ~3.5 L (3.47 kg) of AHU377 free acid isopropyl acetate solution is added 1.984 kg (4.556 mmol) of Valsartan and 40 L of acetone. The reaction mixture is stirred at 23±3° C. to obtain a clear solution which is filtered into a reactor. To the reaction mixture is added a solution of 547.6 g (13.690 mmol) of NaOH in 1.0 L of water at 23±3° C. (which was pre-cooled to 20±5° C. and in-line filtered) over a period of 15-30 min while maintaining the internal temperature at 20-28° C. (slightly exothermic). The flask is rinsed with 190 mL of water and added into the reaction mixture. The reaction mixture is stirred at 23±3° C. for 15 min and a slurry of 4.0 g of [valsartan ((2R,4S)-5-biphenyl-4-yl-4-(3-carboxy-propionylamino)-2-methyl-pentanoic acid ethyl ester)]Na_3.2.5 H_2O seeds in 50 mL of isopropyl acetate is added. The mixture is stirred at 23±3° C. for 2 h to obtain a suspension. The suspension is heated to an internal temperature at 40±3° C. over a period of 20 min and 20 L of isopropyl acetate is added over a period of 20 min while maintaining the internal temperature at 40±3° C. The suspension is stirred at this temperature for an additional 30 min. The mixture is concentrated at an internal temperature at 35±5° C. (T_j 45±5° C.) under reduced pressure (200-350 mbar) to ~35 L of a white slurry (solvent collected: ~25 L). Then 30 L of isopropyl acetate is added the mixture is concentrated at an internal temperature at 35±5° C. (T_j 45±5° C.) under reduced pressure (100-250 mbar) to ~30 L of a white slurry (solvent collected: ~40 L). Again 40 L of isopropyl acetate is added and the mixture is concentrated at an internal temperature at 35±5° C. (T_j 45±5° C.) under reduced pressure (100-200 mbar) to ~30 L of a white slurry (solvent collected: ~30 L). The reaction mixture is cooled to 23±3° C. over ~20 min and stirred at this temperature for an additional 3 h. The solid is collected by filtration under nitrogen over a polypropylene pad on Büchner funnel. The solid is washed with 2×5 L of isopropyl acetate and dried at 35° C. under reduced pressure (20 mbar) until isopropyl acetate content <0.5% to afford the above product as a white solid.

Characterization revealed the same product as in Example 1.

X-Ray Powder Diffraction

Calculation of the interlattice plane intervals from the X-ray powder pattern taken with a Scintag XDS2000 powder diffractometer for the most important lines for the sample give the following results:

d in [Å]: 21.2 (s), 17.0 (w), 7.1 (s), 5.2 (w), 4.7 (w), 4.6 (w), 4.2 (w), 3.5 (w), 3.3 (w)

The error margin for all interlattice plane intervals is ±0.1 Å. The intensities of the peaks are indicated as follows: (w)=weak; (m)=medium; and (st)=strong.

Average values 2Θ in [°] are indicated (error limit of ±0.2) 4.5, 5.5, 5.6, 9.9, 12.8, 15.7, 17.0, 17.1, 17.2, 18.3, 18.5, 19.8, 21.5, 21.7, 23.2, 23.3, 24.9, 25.3, 27.4, 27.9, 28.0, 30.2.

Elemental Analysis

Elemental analysis gives the following measured values of the elements present in the sample. The findings of the elemental analysis, within the error limits, correspond to the overall formula of $(C_{48}H_{55}N_5O_8Na_3)$*2.5H_2O

Found	C: 60.05%	H: 6.24%	N: 8.80%
Calculated*	C: 60.18%	H: 6.31%	N: 8.77%

Infrared Spectroscopy

The infrared absorption spectrum for the sample obtained using Attenuated Total Reflection Fourier Transform Infrared (ATR-FTIR) spectrometer (Nicolet Magna-IR 560) shows the following significant bands, expressed in reciprocal wave numbers (cm^{-1}):

2956 (w), 1711 (st), 1637 (st), 1597 (st), 1488 (w), 1459 (m), 1401 (st), 1357 (w), 1295 (m), 1266 (m), 1176 (w), 1085 (m), 1010 (w), 942 (w), 907 (w), 862 (w), 763 (st), 742 (m), 698 (m), 533 (st).

The error margin for all absorption bands of ATR-IR is ±2 cm^{-1}.

The intensities of the absorption bands are indicated as follows: (w)=weak; (m)=medium; and (st)=strong intensity.

Raman Spectroscopy

Raman spectrum of the sample measured by dispersive Raman spectrometer with 785 nm laser excitation source (Kaiser Optical Systems, Inc.) shows the following significant bands expressed in reciprocal wave numbers (cm^{-1}):

3061 (m), 2930 (m, broad), 1612 (st), 1523 (m), 1461 (w), 1427 (w), 1287 (st), 1195 (w), 1108 (w), 11053 (w), 1041 (w), 1011 (w), 997 (m), 866 (w), 850 (w), 822 (w), 808 (w),

735 (w), 715 (w), 669 (w), 643 (w), 631 (w), 618 (w), 602 (w), 557 (w), 522 (w), 453 (w), 410 (w), 328 (w).

The error margin for all Raman bands is ±2 cm^{-1}.

The intensities of the absorption bands are indicated as follows: (w)=weak; (m)=medium; and (st)=strong intensity.

High Resolution CP-MAS ^{13}C NMR Spectroscopy

The samples are investigated by high resolution CP-MAS (Cross Polarization Magic Angle Spinning)^{13}C NMR spectroscopy using a Bruker-BioSpin AVANCE 500 NMR spectrometer equipped with a 300 Watt high power ^{1}H, two 500 Watt high power X-amplifiers, necessary high power preamplifiers, a "MAS" controller and a 4 mm BioSolids high resolution Bruker probe.

Each sample is packed in a 4 mm ZrO_2 rotor. Critical experimental parameters are 3 msec ^{1}C contact times, 12 KHz spinning speed at the magic angle, a "ramped" contact time, using a "SPINAL64" ^{1}H decoupling scheme, a recycle delay of 10 secs and 1024 scans at 293 deg K. The chemical shifts are referenced with respect to an external Glycine carbonyl at 176.04 ppm.

High resolution CP-MAS ^{13}C NMR shows the following significant peaks (ppm):

179.0, 177.9 177.0, 176.7, 162.0, 141.0, 137.2, 129.6, 129.1, 126.7, 125.3, 64.0, 61.5, 60.4, 50.2, 46.4, 40.6, 38.6, 33.5, 32.4, 29.8, 28.7, 22.3, 20.2, 19.1, 17.8, 16.8, 13.1, 12.1, 11.1.

A physical mixture of individual Na salts of Valsartan and (2R,4S)-5-biphenyl-4-yl-4-(3-carboxy-propionylamino)-2-methyl-pentanoic acid ethyl ester revealed a simple inert mixture of the two salts. However, the sample of the complex prepared in Example 1 exhibited distinctly different spectral features in comparison to a 1:1 mixture of the sodium salts.

DSC and TGA

As measured by differential scanning calorimetry (DSC) using Q1000 (TA Instruments) instrument, the melting onset temperature and the peak maximum temperature for the sample is observed at 139° C. and 145° C., respectively.

As shown by DSC and thermogravimetric analysis (TGA), upon heating, the water of hydration is released in two steps: the first step occurs below 100° C. and the second step above 120° C.

Both DSC and TGA instruments are operated at a heating rate of 10 K/min.

Example 4

Preparation of Linked Pro-Drug of Scheme (1)

Linked pro-drug of valsartan calcium salt and (2R,4S)-5-biphenyl-4-yl-4-(3-carboxy-propionylamino)-2-methyl-pentanoic acid ethyl ester is prepared at room temperature by dissolving 114 mg of the calcium salt of valsartan and 86 mg of (2R,4S)-5-biphenyl-4-yl-4-(3-carboxy-propionylamino)-2-methyl-pentanoic acid ethyl ester free acid in 2 mL methanol, followed by methanol evaporation. The glassy solid residue is then charged with 3 mL of acetonitrile and equilibrated by 10 min. sonication, followed by 20 hours of magnetic stirring. Approximately 120 mg of white solids are collected by filtration. Liquid chromatography (LC) and elemental analysis indicate 1:1 ratio between (2R,4S)-5-biphenyl-4-yl-4-(3-carboxy-propionylamino)-2-methyl-pentanoic acid ethyl ester and valsartan. The sample is amorphous by X-ray powder diffraction.

Preparation of Linked Pro-Drug of Scheme (2)

Linked pro-drug of valsartan calcium salt and (2R,4S)-5-biphenyl-4-yl-4-(3-carboxy-propionylamino)-2-methyl-pentanoic acid ethyl ester and Tris is prepared at room temperature by dissolving 57 mg of the calcium salt of valsartan, 43 mg of (2R,4S)-5-biphenyl-4-yl-4-(3-carboxy-propionylamino)-2-methyl-pentanoic acid ethyl ester free acid, and 12.6 mg of tris(hydroxymethyl)aminomethane (Tris) in 2 mL methanol, followed by methanol evaporation. The glassy solid residue is then charged with 3 mL of acetonitrile and equilibrated by 10 min. sonication, followed by 20 hours of magnetic stirring. Approximately 83 mg of white solids are collected by filtration. LC and elemental analysis indicate 1:1 ratio between (2R,4S)-5-biphenyl-4-yl-4-(3-carboxy-propionylamino)-2-methyl-pentanoic acid ethyl ester and valsartan. The sample is amorphous by X-ray powder diffraction.

While the invention has been described above with reference to specific embodiments thereof, it is apparent that many changes, modifications, and variations can be made without departing from the inventive concept disclosed herein. Accordingly, it is intended to embrace all such changes, modifications and variations that fall within the spirit and broad scope of the appended claims. All patent applications, patents, and other publications cited herein are incorporated by reference in their entirety.

What is claimed is:

1. An amorphous solid form of a compound comprising anionic (S)-N-valeryl-N-{[2'-(1H-tetrazole-5-yl)-biphenyl-4-yl]-methyl}-valine, anionic (2R,4S)-5-biphenyl-4-yl-4-(3-carboxy-propionylamino)-2-methyl-pentanoic acid ethyl ester, and sodium cations in a 1:1:3 molar ratio.

2. A pharmaceutical composition comprising the amorphous solid form according to claim 1 and at least one pharmaceutically acceptable excipient.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 11,096,918 B2
APPLICATION NO. : 16/579581
DATED : August 24, 2021
INVENTOR(S) : Lili Feng et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

On the Title Page

Item [56]

Page 2
Column 2:
Line 33, "Compounts" should read --Compounds--;
Line 48, "acis" should read --acid--; and
Line 50, "72(2): 193-200, 1992." should read --22(2): 193-200, 1992.--.

Page 3
Column 2:
Line 2, "High-Throughout" should read --High-Throughput--.

Page 5
Column 1:
Line 17, "vol 101," (2nd occurrence) should be deleted;
Line 20, "2000"Crystal" should read --2000", Crystal--; and
Line 27, "Aakeröy,Christer" should read --Aakeröy, Christer--.

Column 2:
Line 34, "People Health" should read --People's Health--;
Line 52, "Anatriuretic" should read --A natriuretic--;
Line 62, "ad Evaluation Carbolinium" should read --and Evaluation of β-Carbolinium--; and
Line 63, "on Delocalized" should read --on π-Delocalized--.

Page 6
Column 2:
Line 2, "Part IX.t" should read --Part IX--; and
Line 5, "Sodium IMitrophenolate" should read --sodium *o*-nitrophenolate--.

Signed and Sealed this
First Day of February, 2022

Drew Hirshfeld
Performing the Functions and Duties of the Under Secretary of Commerce for Intellectual Property and Director of the United States Patent and Trademark Office

CERTIFICATE OF CORRECTION (continued)
U.S. Pat. No. 11,096,918 B2

In the Specification

Column 3:
Line 65, "methyl-phenyl)propionyl]-methionine)" should read
--methylphenyl)propionyl]-methionine--.

Column 5:
Line 34, "((1 S,3R) –1-biphenyl-4-y lmethyl-3-ethoxy carbonyl" should read
--((1S,3R)-1-biphenyl-4-ylmethyl-3-ethoxycarbonyl--;
Line 35, "butylcarbamoyl)propionate-(S)-3 '-methyl-2'-(pentanoyl-" should read
--butylcarbamoyl)propionate-(S)-3'-methyl-2'-(pentanoyl--; and
Line 36, "{2 "-(tetrazol-5-ylate)biphenyl-4'-y 'methyl} amino)bu-" should read
--2"-(tetrazol-5-ylate)biphenyl-4'-ylmethyl}amino)bu- --.

Column 15:
Line 15, "is may" should read --may--; and
Line 46, "species" should read --species.--.

Column 16:
Line 63, "onate-(S)-3'-methyl-2'-(pentanoyl{22"-(tetrazol-5-ylate)bi-" should read
--onate-(S)-3'-methyl-2'-(pentanoyl{2"-(tetrazol-5-ylate)bi- --.

Column 18:
Line 62, "[3-((1 S,3R)-1-biphenyl-4-ylmethyl-3-ethoxycarbonyl-1-" should read
--[3-((1S,3R)-1-biphenyl-4-ylmethyl-3-ethoxycarbonyl-1- --; and
Line 64, "onate-(S)-3'-methyl-2'-(pentanoyl{22"-(tetrazol-5-ylate)bi-" should read
--onate-(S)-3'-methyl-2'-(pentanoyl{2"-(tetrazol-5-ylate)bi- --.

Column 19:
Line 25, "onate-(S)-3'-methyl-2'-(pentanoyl{22"-(tetrazol-5-ylate)bi-" should read
--onate-(S)-3'-methyl-2'-(pentanoyl{2"-(tetrazol-5-ylate)bi- --; and
Line 64, "und γ." should read --and γ.--.

Column 22:
Line 43, "met-formin;" should read --metformin;--; and
Line 62, "3-adrenergic" should read --β-adrenergic--.

Column 23:
Line 23, "in addition a" should read --in addition to a--;
Line 34, "[3-((1 S,3R)-1-biphenyl-4-ylmethyl-3-ethoxycarbonyl-1" should read
--[3-((1S,3R)-1-biphenyl-4-ylmethyl-3-ethoxycarbonyl-1- --;
Line 43, "ylate)biphenyl-4'-ylmethyl}amino) butyrate]" should read
--ylate)biphenyl-4'-ylmethyl}amino)butyrate]--; and
Line 60, "bamoyl)propionate-(S)-3'-methyl-2'-(pentanoyl{22"-(tetra-" should read
--bamoyl)propionate-(S)-3'-methyl-2'-(pentanoyl{2"-(tetra- --.

CERTIFICATE OF CORRECTION (continued)
U.S. Pat. No. 11,096,918 B2

Column 24:
Line 30, "propionate-(S)-3′-methyl-2′-(pentanoyl{22″-(tetrazol-5-" should read --propionate-(S)-3′-methyl-2′-(pentanoyl{2″-(tetrazol-5- --.

Column 28:
Line 25, "or he" should read --or the--; and
Line 43, "ester)]Na_3.2.5 H_2O" should read --ester)]Na_3•2.5 H_2O--.

Column 29:
Line 5, "ester)]Na_3.2.5 H_2O" should read --ester)]Na_3•2.5 H_2O--;
Line 37, "ester)]Na_3.2.5 H_2O" should read --ester)]Na_3•2.5 H_2O--; and
Line 15, "(8 mL) water" should read --(8 mL)--.

Column 30:
Line 6, "added" should read --added and--; and
Line 40, "($C_{48}H_{55}N_6O_8Na_3$)*2.5H_2O" should read --($C_{48}H_{55}N_6O_8Na_3$)•2.5H_2O--.

Column 31:
Line 14, "1^3C" should read --^{13}C--.

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

NOVARTIS PHARMACEUTICALS CORPORATION, Plaintiff, v. ALEMBIC PHARMACEUTICALS LIMITED, ALEMBIC GLOBAL HOLDING SA, ALEMBIC PHARMACEUTICALS, INC., CRYSTAL PHARMACEUTICAL (SUZHOU) CO., LTD., MSN PHARMACEUTICALS INC., MSN LABORATORIES PRIVATE LIMITED, MSN LIFE SCIENCES PRIVATE LIMITED, MYLAN PHARMACEUTICALS INC., MYLAN LABORATORIES LIMITED, VIATRIS INC., NANJING NORATECH PHARMACEUTICAL CO., LIMITED, Defendants.	C.A. No. _____

COMPLAINT

Novartis Pharmaceuticals Corporation ("Novartis"), by its attorneys, hereby alleges as follows:

NATURE OF THE ACTION

1. This is a patent infringement action arising under Title 35 of the United States Code and concerning Abbreviated New Drug Applications ("ANDAs") submitted to the United States Food and Drug Administration ("FDA") by the above-named Defendants seeking FDA approval to engage in the commercial manufacture, use, sale, offer for sale, and/or importation of sacubitril/valsartan tablets, generic versions of Novartis's ENTRESTO® tablets, 24 mg/26 mg,

49 mg/51 mg, and 97 mg/103 mg, prior to the expiration of U.S. Patent No. 11,096,918 (the "'918 patent").

PARTIES

A. Novartis

2. Novartis Pharmaceuticals Corporation is a corporation organized and existing under the laws of the State of Delaware, having a principal place of business in East Hanover, New Jersey.

B. Defendants

a. Alembic Pharmaceuticals Limited; Alembic Global Holding SA; Alembic Pharmaceuticals, Inc. (ANDA No. 213682)

3. On information and belief, Alembic Pharmaceuticals Limited is a corporation organized and existing under the laws of India, having a principal place of business at Alembic Road, Vadodara, Gujarat, India 390003.

4. On information and belief, Alembic Global Holding SA is a corporation organized and existing under the laws of Switzerland, having a principal place of business at Rue Fritz-Courvoisier 40, 2300 La Chaux-de-Fonds, Switzerland. On information and belief, Alembic Global Holding SA is a wholly owned subsidiary of Alembic Pharmaceuticals Limited.

5. On information and belief, Alembic Pharmaceuticals, Inc. is a corporation organized and existing under the laws of the State of Delaware, having a registered agent for the service of process at National Registered Agents, Inc., 160 Greentree Drive, Suite 101, Dover, Delaware 19904, and having a principal place of business at 750 Route 202, Bridgewater, New Jersey 08807. On information and belief, Alembic Pharmaceuticals, Inc. is a wholly owned subsidiary of Alembic Global Holding SA.

6. On information and belief, Alembic Pharmaceuticals Limited develops, manufactures, distributes, sells, and/or imports drug products for the entire United States market and does business in every state including Delaware, either directly or indirectly.

7. On information and belief, Alembic Global Holding SA develops, manufactures, distributes, sells, and/or imports drug products for the entire United States market and does business in every state including Delaware, either directly or indirectly.

8. On information and belief, Alembic Pharmaceuticals, Inc., manufactures, distributes, sells, and/or imports drug products for the entire United States market and does business in every state including Delaware, either directly or indirectly.

9. On information and belief, Alembic Pharmaceuticals Limited has submitted to the FDA ANDA No. 213682 for sacubitril/valsartan tablets, 24 mg/26 mg, 49 mg/51 mg, and 97 mg/103 mg ("Alembic ANDA Products"), seeking FDA approval to engage in the commercial manufacture, use, sale, offer for sale, and/or importation of the Alembic ANDA Products in or into the United States, including Delaware, prior to the expiration of the '918 patent.

10. Alembic Pharmaceuticals Limited has committed an act of infringement in this judicial district by filing ANDA No. 213682 with the intent to make, use, sell, offer for sale, and/or import the Alembic ANDA Products in or into this judicial district, prior to the expiration of the '918 patent, an act of infringement that has led and will lead to foreseeable harm and injury to Novartis, a Delaware corporation.

11. On information and belief, Alembic Global Holding SA acted in concert with and under the direction of Alembic Pharmaceuticals Limited, and acted in concert with and directed Alembic Pharmaceuticals, Inc., in the preparation and submission of ANDA No. 213682, and, if the ANDA is approved, will act in concert with and under the direction of Alembic

Pharmaceuticals Limited, and will act in concert with and direct Alembic Pharmaceuticals, Inc., to engage in the commercial manufacture, use, sale, offer for sale, and/or importation of the Alembic ANDA Products in or into the United States, including Delaware, prior to the expiration of the '918 patent.

12. On information and belief, Alembic Pharmaceuticals, Inc. acted in concert with and under the direction of Alembic Pharmaceuticals Limited and/or Alembic Global Holding SA in the preparation and submission of ANDA No. 213682, and, if the ANDA is approved, will act in concert with and under the direction of Alembic Pharmaceuticals Limited and/or Alembic Global Holding SA to engage in the commercial manufacture, use, sale, offer for sale, and/or importation of the Alembic ANDA Products in or into the United States, including Delaware, prior to the expiration of the '918 patent.

13. Alembic Pharmaceuticals Limited, by itself or together with Alembic Global Holding SA and/or Alembic Pharmaceuticals, Inc., has taken the costly, significant step of applying to the FDA for approval to engage in future activities, including the marketing of the Alembic ANDA Products, that will be purposefully directed at Delaware and elsewhere.

14. On information and belief, Alembic Pharmaceuticals Limited has systematic and continuous contacts with Delaware; has established distribution channels for drug products in Delaware; regularly and continuously conducts business in Delaware, including by selling drug products in Delaware either directly or indirectly through subsidiaries, agents, or affiliates, including Alembic Pharmaceuticals, Inc.; has purposefully availed itself of the privilege of doing business in Delaware; and derives substantial revenue from the sale of drug products in Delaware.

15. Alembic Pharmaceuticals Limited, Alembic Global Holding SA, and Alembic Pharmaceuticals, Inc. have availed themselves of the legal protections of the State of Delaware by, among other things, admitting jurisdiction and asserting counterclaims in lawsuits filed in the United States District Court for the District of Delaware. *See, e.g.*, *CyDex Pharm. Inc. v. Alembic Global Holding SA et al.*, C.A. No. 19-956 (D. Del.); *Otsuka Pharm. Co., Ltd. et al. v. Alembic Pharm. Ltd. et al.*, C.A. No. 19-2007 (D. Del.); *Astrazeneca AB et al. v. Alembic Pharm. Ltd. et al.*, C.A. No. 20-202 (D. Del.); *Abbvie Inc. et al. v. Alembic Pharm. Ltd. et al.*, C.A. No. 20-968; *Otsuka Pharm. Co., Ltd. et al. v. Alembic Pharm. Ltd. et al.*, C.A. No. 20-1365; *Novartis Pharm. Corp. v. Alembic Pharm. Ltd. et al.*, C.A. No. 20-74 (D. Del.).

16. Alembic Pharmaceuticals Limited, the entity that, on information and belief, submitted ANDA No. 213682, has agreed with Novartis to litigate any patent action(s) concerning ANDA No. 213682 in the District of Delaware, and has agreed, only for the purposes of such action(s), not to challenge personal jurisdiction and venue in the District of Delaware.

b. Crystal Pharmaceutical (Suzhou) Co., Ltd. (ANDA No. 213605)

17. On information and belief, Crystal Pharmaceutical (Suzhou) Co., Ltd. ("Crystal") is a corporation organized and existing under the laws of China, having a principal place of business at B4-101, Biological Nano Park, No. 218, Xinghu Street, Suzhou Industrial Park, China.

18. On information and belief, Crystal develops, manufactures, distributes, sells, and/or imports drugs for the entire United States market and does business in every state including Delaware, either directly or indirectly.

19. On information and belief, Crystal has submitted to the FDA ANDA No. 213605 for sacubitril/valsartan tablets, 24 mg/26 mg, 49 mg/51 mg, and 97 mg/103 mg ("Crystal ANDA

Products"), seeking FDA approval to engage in the commercial manufacture, use, sale, offer for sale, and/or importation of the Crystal ANDA Products in or into the United States, including Delaware, prior to the expiration of the '918 patent.

20. Crystal has committed an act of infringement in this judicial district by filing ANDA No. 213605 with the intent to make, use, sell, offer for sale, and/or import the Crystal ANDA Products in or into this judicial district, prior to the expiration of the '918 patent, an act of infringement that has led and will lead to foreseeable harm and injury to Plaintiff Novartis, a Delaware corporation.

21. Crystal has taken the costly, significant step of applying to the FDA for approval to engage in future activities, including the marketing of the Crystal ANDA Products, that will be purposefully directed at Delaware and elsewhere.

22. On information and belief, Crystal has systematic and continuous contacts with Delaware; has established distribution channels for drug products in Delaware; regularly and continuously conducts business in Delaware, including by selling drug products in Delaware, either directly or indirectly through its subsidiaries, agents, or affiliates; has purposefully availed itself of the privilege of doing business in Delaware; and derives substantial revenue from the sale of drug products in Delaware.

23. Crystal has availed itself of the legal protections of the State of Delaware by, among other things, admitting jurisdiction and asserting counterclaims in lawsuits filed in the United States District Court for the District of Delaware. *See, e.g.*, *Novartis Pharm. Corp. v. Alkem Labs. Ltd. et al.*, C.A. No. 19-1979 (D. Del.); *Neurocrine Biosciences, Inc. v. Crystal Pharm. (Suzhou) Co., Ltd.*, C.A. No. 21-1464 (D. Del.); *Novartis Pharm. Corp. v. Crystal Pharm. (Suzhou) Co., Ltd.*, C.A. No. 21-1452 (D. Del.).

24. Crystal, the entity that, on information and belief, submitted ANDA No. 213605, has agreed with Novartis to litigate any patent action(s) concerning ANDA No. 213605 in the District of Delaware, and has agreed, only for the purposes of such action(s), not to challenge personal jurisdiction and venue in the District of Delaware.

c. MSN Pharmaceuticals Inc.; MSN Laboratories Private Limited; MSN Life Sciences Private Limited (ANDA No. 213748)

25. On information and belief, MSN Pharmaceuticals Inc. is a corporation organized and existing under the laws of the State of Delaware, having a registered agent for the service of process at United States Corporation Agents, Inc., 300 Delaware Avenue, Suite 210-A, Wilmington, Delaware 19801, and having a principal place of business at 20 Duke Road, Piscataway, New Jersey 08854. On information and belief, MSN Pharmaceuticals Inc. is a wholly owned subsidiary of and U.S. agent for MSN Laboratories Private Limited.

26. On information and belief, MSN Laboratories Private Limited is a corporation organized and existing under the laws of India, having a principal place of business at MSN House, C-24, Sanathnagar Industrial Estate, Hyderabad, 500018, Telangana, India.

27. On information and belief, MSN Life Sciences Private Limited is a corporation organized and existing under the laws of India, having a principal place of business at Sy No - 21/A & 21AA, Mambapur (Village), Gummadidala (Mandal), Sangareddy (District) - 502313, Telangana, India. On information and belief, MSN Life Sciences Private Limited is a wholly owned subsidiary of MSN Laboratories Private Limited.

28. On information and belief, MSN Pharmaceuticals Inc. develops, manufactures, distributes, sells, and/or imports drug products for the entire United States market and does business in every state including Delaware, either directly or indirectly.

29. On information and belief, MSN Laboratories Private Limited develops, manufactures, distributes, sells, and/or imports drug products for the entire United States market and does business in every state including Delaware, either directly or indirectly.

30. On information and belief, MSN Life Sciences Private Limited develops, manufactures, distributes, sells, and/or imports drug products for the entire United States market and does business in every state including Delaware, either directly or indirectly.

31. On information and belief, MSN Pharmaceuticals Inc. and MSN Laboratories Private Limited have submitted to the FDA ANDA No. 213748 for sacubitril/valsartan tablets, 24 mg/26 mg, 49 mg/51 mg, and 97 mg/103 mg ("MSN ANDA Products"), seeking FDA approval to engage in the commercial manufacture, use, sale, offer for sale, and/or importation of the MSN ANDA Products in or into the United States, including Delaware, prior to the expiration of the '918 patent.

32. MSN Pharmaceuticals Inc. and MSN Laboratories Private Limited have committed an act of infringement in this judicial district by filing ANDA No. 213748 with the intent to make, use, sell, offer for sale, and/or import the MSN ANDA Products in or into this judicial district, prior to the expiration of the '918 patent, an act of infringement that has led and will lead to foreseeable harm and injury to Novartis, a Delaware corporation.

33. On information and belief, MSN Pharmaceuticals Inc. acted in concert with and under the direction of MSN Laboratories Private Limited, and acted in concert with MSN Life Sciences Private Limited, in the preparation and submission of ANDA No. 213748, and, if the ANDA is approved, will act in concert with and under the direction of MSN Laboratories Private Limited, and will act in concert with MSN Life Sciences Private Limited, to engage in the commercial manufacture, use, sale, offer for sale, and/or importation of the MSN ANDA

Products in or into the United States, including Delaware, prior to the expiration of the '918 patent.

34. On information and belief, MSN Life Sciences Private Limited acted in concert with and under the direction of MSN Laboratories Private Limited, and acted in concert with MSN Pharmaceuticals Inc., in the preparation and submission of ANDA No. 213748, and, if the ANDA is approved, will act in concert with and under the direction of MSN Laboratories Private Limited, and will act in concert with MSN Pharmaceuticals Inc., to engage in the commercial manufacture, use, sale, offer for sale, and/or importation of the MSN ANDA Products in or into the United States, including Delaware, prior to the expiration of the '918 patent.

35. MSN Pharmaceuticals Inc. and MSN Laboratories Private Limited, by themselves or together with MSN Life Sciences Private Limited, have taken the costly, significant step of applying to the FDA for approval to engage in future activities, including the marketing of the MSN ANDA Products, that will be purposefully directed at Delaware and elsewhere.

36. On information and belief, MSN Laboratories Private Limited has systematic and continuous contacts with Delaware; has established distribution channels for drug products in Delaware; regularly and continuously conducts business in Delaware, including by selling drug products in Delaware, either directly or indirectly through its subsidiaries, agents, or affiliates, including MSN Pharmaceuticals Inc.; has purposefully availed itself of the privilege of doing business in Delaware; and derives substantial revenue from the sale of drug products in Delaware.

37. On information and belief, MSN Life Sciences Private Limited has systematic and continuous contacts with Delaware; has established distribution channels for drug products in Delaware; regularly and continuously conducts business in Delaware, including by selling drug

products in Delaware, either directly or indirectly through its subsidiaries, agents, or affiliates, including MSN Pharmaceuticals Inc.; has purposefully availed itself of the privilege of doing business in Delaware; and derives substantial revenue from the sale of drug products in Delaware.

38. MSN Pharmaceuticals Inc. and MSN Laboratories Private Limited have availed themselves of the legal protections of the State of Delaware by, among other things, admitting jurisdiction and asserting counterclaims in lawsuits filed in the United States District Court for the District of Delaware. *See, e.g.*, *Vanda Pharm. v. MSN Pharm. Inc. et al.*, C.A. No. 19-926 (D. Del.), *Novartis Pharm. Corp. v. Dr. Reddy's Labs., Inc. et al.*, C.A. No. 19-2053 (D. Del.), *Exelixis, Inc. v. MSN Labs. Private Ltd. et al.*, C.A. No. 20-633 (D. Del.).

39. MSN Pharmaceuticals Inc. and MSN Laboratories Private Limited, the entities that, on information and belief, submitted ANDA No. 213748, have agreed with Novartis to litigate any patent action(s) concerning ANDA No. 213748 in the District of Delaware, and have agreed, only for the purposes of such action(s), not to challenge personal jurisdiction and venue in the District of Delaware.

d. Mylan Pharmaceuticals Inc.; Mylan Laboratories Limited; Viatris Inc. (collectively, the "Mylan Defendants") (ANDA No. 213646)

40. On information and belief, Mylan Pharmaceuticals Inc. is a corporation organized under the laws of the State of West Virginia, purporting to have a principal place of business at 3711 Collins Ferry Road, Morgantown, West Virginia 26505. On information and belief, Mylan Pharmaceuticals Inc. is an agent, affiliate, wholly owned subsidiary and alter ego of Viatris Inc., and subsumed within Viatris Inc.

41. On information and belief, Mylan Laboratories Limited is a corporation organized and existing under the laws of India, having a principal place of business at Plot No. 564/A122, Road No. 92, Jubilee Hills, Hyderabad 500034, India. On information and belief, Mylan Laboratories Limited is a wholly owned subsidiary of Viatris Inc., and an agent and affiliate of Mylan Pharmaceuticals Inc. and Viatris Inc.

42. On information and belief, Viatris Inc. is a corporation organized and existing under the laws of Delaware, having a principal place of business at 1000 Mylan Blvd., Canonsburg, Pennsylvania, 15317.

43. On information and belief, Viatris Inc.'s website states that "Viatris was formed in 2020 through the combination of Mylan and Upjohn, a legacy division of Pfizer. By integrating the strengths of these two companies, including our approximately 37,000 colleagues globally, we aim to deliver increased access to affordable, quality medicines for patients worldwide. Our global portfolio includes . . . generics, including branded and complex generics . . . . We are headquartered in the United States . . . . As we work to fully transition to the Viatris brand commercially and operationally around the world, you may continue to see both the Mylan and Upjohn names in certain markets." (https://www.viatris.com/en/about-us/our-story (last visited October 24, 2022)).

44. On information and belief, any corporate separateness that existed between Viatris Inc. and Mylan Pharmaceuticals Inc. shortly after Viatris Inc. was formed has dissolved, and Mylan Pharmaceuticals Inc. is now no more than an alter ego for Viatris Inc.

45. On information and belief, Viatris Inc. is working to fully transition the Viatris brand commercially and operationally around the world, and as a result, Viatris Inc. has been methodically divesting Mylan Pharmaceuticals Inc. properties, assuming corporate

responsibilities of Mylan Pharmaceuticals Inc., adopting employees of Mylan Pharmaceuticals Inc., commingling funds with Mylan Pharmaceuticals Inc., and subsuming Mylan Pharmaceuticals Inc. into Viatris Inc. For example, on information and belief, as of March 7, 2022, Viatris Inc. closed Mylan Pharmaceuticals Inc.'s facility located at 781 Chestnut Ridge Road, Morgantown, West Virginia, 26505 and auctioned off its equipment. (*See, e.g.*, https://www.wboy.com/news/local/monongalia-and-preston/former-mylan-viatris-facility-auctions-off-equipment/ (last visited October 24, 2022); https://www.hgpauction.com/auctions/110662/viatris-morgantown-2/ (last visited October 24, 2022)). On information and belief, on March 31, 2022, West Virginia University took ownership of 781 Chestnut Ridge Road, Morgantown, West Virginia, 26505. (*See, e.g.*, https://www.wdtv.com/2022/03/31/wvu-purchases-former-mylan-plant/ (last visited October 24, 2022)). On information and belief, Viatris Inc. sold this property to West Virginia University. (*Id.*)

46. On information and belief, Robert J. Coury, formerly the executive chairman of Mylan, is now the executive chairman of Viatris Inc. following the completion of the $27 billion combination of Mylan with Pfizer's Upjohn business to create Viatris Inc. (https://www.viatris.com/en/about-us/our-leaders/robert-j-coury (last visited on October 24, 2022)). On information and belief, Mr. Coury "leads the [Viatris Inc.] board of directors, oversees the strategic direction of the company in collaboration with executive management, and advises the management team as they execute on the company's strategy to drive value creation . . ." (*Id.*)

47. On information and belief, Viatris Inc. shares with or has subsumed one or more corporate officers and employees of Mylan Pharmaceuticals Inc. (*See, e.g.*,

https://www.fiercepharma.com/pharma/mylan-crowns-former-ceo-coury-as-executive-chairman-as-upjohn-merger-deal-faces-delays (last visited October 24, 2022); https://www.viatris.com/en/about-us/our-leaders (last visited October 24, 2022); https://www.wsj.com/market-data/quotes/VTRS/company-people/executive-profile/268055 (last visited October 24, 2022); https://www.sec.gov/Archives/edgar/data/1792044/000119312521313437/d163117ddef14a.htm (last visited October 24, 2022)). On information and belief, Viatris Inc.'s sharing or subsuming of Mylan Pharmaceuticals Inc.'s corporate officers and employees demonstrates that Mylan Pharmaceuticals Inc. is an alter ego of and subsumed within Viatris Inc.

48. On information and belief, the shared or subsumed officers of Mylan Pharmaceuticals Inc. maintain their offices at the same place of business as Viatris Inc.'s principal place of business at 1000 Mylan Blvd., Canonsburg, Pennsylvania, 15317. (*See, e.g.*, https://www.sec.gov/Archives/edgar/data/1792044/000119312521313437/d163117ddef14a.htm (last visited October 24, 2022)). On information and belief, Viatris Inc.'s and Mylan Pharmaceuticals Inc.'s use of the same office or business location demonstrates that Mylan Pharmaceuticals Inc. is an alter ego of and subsumed within Viatris Inc.

49. On information and belief, upon the combination of Mylan and Upjohn, Viatris Inc. assumed certain retention agreements and retirement benefit agreements between Mylan and certain of its officers. (*See, e.g.*, https://www.sec.gov/Archives/edgar/data/1792044/000119312521313437/d163117ddef14a.htm (last visited October 24, 2022)).

50. On information and belief, Mylan Pharmaceuticals Inc. holds itself out to the public as "Mylan Pharmaceuticals Inc., a Viatris company." (*See, e.g.*,

https://newsroom.viatris.com/2022-01-18-Mylan-Pharmaceuticals-Inc-,-a-Viatris-Company,-Conducting-Voluntary-Recall-of-One-Batch-of-Semglee-R-insulin-glargine-injection-,-100-units-mL-U-100-,-3-mL-Prefilled-Pens,-Due-to-the-Potential-for-a-Missing-Label-in-the-Batch (last visited October 24, 2022)). On information and belief, Mylan Pharmaceuticals Inc.'s holding itself out as Viatris Inc. demonstrates that Mylan Pharmaceuticals Inc. is an alter ego of and subsumed within Viatris Inc.

51. On information and belief, as Mylan entities, including Mylan Pharmaceuticals Inc., are now part of Viatris Inc., attempts to access Mylan's website, mylan.com, result in a pop-up window redirecting access to Viatris Inc., along with a statement that: "Mylan is now part of Viatris, a new global healthcare company committed to empowering people to live healthier at every stage of life." (https://www.mylan.com (last visited October 24, 2022)). On information and belief, Mylan's LinkedIn website states: "Follow us on our new journey as Viatris. www.linkedin.com/company/viatris" and "We have combined with Upjohn, a legacy division of Pfizer, and are now Viatris. Follow along on our new journey as we empower people worldwide to live healthier at every stage of life. www.linkedin.com/company/viatris." (https://www.linkedin.com/company/mylan/ (last visited October 24, 2022)). On information and belief, the redirection from mylan.com to the website of Viatris Inc. and Mylan's holding itself out as Viatris Inc. demonstrates that Mylan Pharmaceuticals Inc. is an alter ego of and subsumed within Viatris Inc.

52. On information and belief, Mylan employees are now identified as Viatris Inc. employees. (*See, e.g.*, (https://www.linkedin.com/in/brandon-mcmahon-2754a263/ (last visited October 24, 2022)). On information and belief, the identification of Mylan employees as Viatris

Inc. employees demonstrates that Mylan Pharmaceuticals Inc. is an alter ego of and subsumed within Viatris Inc.

53. On information and belief, current job listings for Mylan Pharmaceuticals Inc. indicate employment is with Viatris Inc., demonstrating that Mylan Pharmaceuticals Inc. is an alter ego of and subsumed within Viatris Inc. (*See, e.g.*, https://www.indeed.com/jobs?q=Mylan%20Pharmaceuticals%20Inc.&l=Morgantown%2C%20WV&from=mobRdr&utm_source=%2Fm%2F&utm_medium=redir&utm_campaign=dt&vjk=8203d5b1e393f80f (last visited October 24, 2022)). On information and belief, the identification of jobs associated with Mylan Pharmaceuticals Inc. as being with Viatris Inc. demonstrates that Mylan Pharmaceuticals Inc. is an alter ego of and subsumed within Viatris Inc.

54. On information and belief, on July 1, 2021, Viatris Inc. entered into a $4.0 billion revolving facility agreement with certain lenders (the "2021 Revolving Facility.") (*See* Viatris Inc. Form 10-K, dated Mar. 1, 2021 (https://www.sec.gov/ix?doc=/Archives/edgar/data/0001792044/000179204421000009/vtrs-20201231.htm (last visited October 24, 2022)). On information and belief, Mylan Pharmaceuticals Inc. has access to the 2021 Revolving Facility. (*Id.*) On information and belief, Viatris Inc. and Mylan Pharmaceuticals Inc. operate as a single entity with the capacity to borrow funds from revolving loan accounts that Viatris Inc. has instituted with certain lenders.

55. On information and belief, Viatris Inc. entered into a two-year $400 million "Receivables Facility" agreement in 2020 which expired in April 2022. (*Id.*) Mylan Pharmaceuticals Inc. "has access to $400 million under the Receivables Facility." (*Id.*) On information and belief, under Viatris Inc.'s Receivables Facility agreement, Mylan Pharmaceuticals Inc., operating as a single entity with Viatris Inc., has the capacity to sell its

accounts receivables to Viatris Inc.'s subsidiary Mylan Securitization LLC for the purpose of accessing instant funds from outstanding unpaid invoices. (*Id.*) On information and belief, Viatris Inc. thereby funds Mylan Pharmaceuticals Inc. through Viatris Inc.'s subsidiary Mylan Securitization LLC. On information and belief, Viatris Inc. and Mylan Pharmaceuticals Inc.'s joint use of the 2021 Revolving Facility and 2020 Receivables Facility demonstrates the commingling of funds and that Mylan Pharmaceuticals Inc. is an alter ego of and subsumed within Viatris Inc.

56. On information and belief, Viatris Inc. agreed to pay $264 million in settlement fees, to resolve class action cases pending in the U.S. District Court for the District of Kansas on behalf of defendants Mylan N.V., Mylan Specialty L.P., Mylan Pharmaceuticals Inc., and Heather Bresch. (*See* Viatris Inc. Form 10-Q, dated May 9, 2022 (https://www.sec.gov/ix?doc=/Archives/edgar/data/0001792044/000179204422000017/vtrs-20220331.htm (last visited October 24, 2022))); *In Re: EpiPen (Epinephrine Injection, USP) Marketing, Sales Practices and Antitrust Litigation*, MDL No. 2785, 17-md-2785-DDC-TJJ (D. Kan. March 11, 2022).) On information and belief, Viatris Inc.'s payment of debt incurred by itself and its subsidiaries demonstrates a commingling of funds between Viatris Inc. and its subsidiaries including Mylan Pharmaceuticals Inc., a lack of corporate separateness, and the various Mylan subsidiaries, including Mylan Pharmaceuticals Inc., being subsumed within Viatris Inc.

57. On information and belief, Viatris Inc.'s 2021 10-K report states that references to "Viatris" therein refer to "Viatris Inc. and its subsidiaries." (Viatris Inc. Form 10-K, dated Mar. 1, 2021 (https://www.sec.gov/ix?doc=/Archives/edgar/data/0001792044/000179204422000010/vtrs-

20211231.htm (last visited October 24, 2022))). Viatris Inc.'s 2021 10-K report identifies Mylan Pharmaceuticals Inc. as a Viatris Inc. subsidiary, and references the "Viatris Charter." (*Id.*) Upon information and belief, the "Viatris Charter" is the "amended and restated certificate of incorporation of Viatris Inc." According to Viatris Inc.'s 2021 10-K report, the Viatris Charter designates Delaware "as the sole and exclusive forum for certain types of actions and proceedings that may be initiated by Viatris' stockholders, which could discourage lawsuits against Viatris and its directors and officers . . . . To the fullest extent permitted by law, this exclusive forum provision will apply to state and federal law claims, including claims under the federal securities laws . . . . This exclusive forum provision may limit the ability of Viatris' stockholders to bring a claim in a judicial forum that such stockholders find favorable for disputes with Viatris or its directors or officers, which may discourage such lawsuits against Viatris or its directors or officers." (*Id.*)

58. On information and belief, Viatris Inc. refers to FDA approvals of ANDAs submitted by Mylan Pharmaceuticals Inc. as Viatris Inc.'s FDA ANDA approvals. (*See, e.g.*, (*See, e.g.*, *Mylan Launches First Generic Restasis. (RX/Generic Drugs)*, CHAIN DRUG REV., Feb. 21, 2022, at 31 ("Rajiv Malik, president of [Mylan Pharmaceuticals Inc.'s] parent company, Viatris Inc., said: 'I am pleased that Viatris has received the first FDA approval for generic Restasis . . . .'" and "Viatris developed markets president Tony Mauro said: 'The approval of generic Restasis reinforces our ongoing commitment to deliver innovative solutions . . . . We look forward to quickly bringing this important product to millions of Americans . . . .'" (https://mydigitalpublication.com/publication/?i=738336&article_id=4212714&view=articleBrowser (last visited October 24, 2022)); *Viatris Inc. Announces Receipt of the First FDA Approval for Generic Version of Symbicort® Inhalation Aerosol, Breyna™ (Budesonide and Formoterol*

Fumarate Dihydrate Inhalation Aerosol), in Partnership with Kindeva ("Viatris President Rajiv Malik added: 'The momentous FDA final approval of Breyna is further evidence of our well-established development expertise and proven ability to move up the value chain with more complex products by leveraging our robust scientific capabilities to target gaps in healthcare and patient needs. This approval also builds on our past successes of bringing other complex products first to market and demonstrates the continued delivery of our strong pipeline.'") (https://newsroom.viatris.com/2022-03-16-Viatris-Inc-Announces-Receipt-of-the-First-FDA-Approval-for-Generic-Version-of-Symbicort-R-Inhalation-Aerosol,-Breyna-TM-Budesonide-and-Formoterol-Fumarate-Dihydrate-Inhalation-Aerosol-,-in-Partnership-with-Kindeva (Mar. 16, 2022) (last visited October 24, 2022).)

59. On information and belief, products identified as products of "Mylan Pharmaceuticals Inc." or "Mylan Pharmaceuticals Inc., a Viatris Company" by the FDA are now identified as products of Viatris Inc. on Viatris Inc.'s website. (*Compare e.g.*, FDA Listing of Authorized Generics as of Oct. 1, 2022 (https://www.fda.gov/media/77725/download (last visited October 24, 2022)) and Viatris Inc.'s Product Catalog (https://www.viatris.com/en-us/lm/countryhome/us-products/productcatalog/ (last visited October 24, 2022))).

60. On information and belief, Viatris Inc.'s 2021 10-K report refers to Viatris Inc. and its subsidiaries as "the Company" and identifies Mylan Pharmaceuticals Inc. as a "wholly owned subsidiary." (Viatris Inc. Form 10-K, dated Mar. 1, 2021 (https://www.sec.gov/ix?doc=/Archives/edgar/data/0001792044/000179204422000010/vtrs-20211231.htm (last visited October 24, 2022))). According to the report, "Viatris invests significant sums in R&D and in manufacturing capacity. [Viatris] also often incur[s] substantial litigation expense as a result of defending or challenging brand patents or exclusivities . . . " (*Id.*)

Viatris Inc.'s 2021 10-K report further states that "[t]he Company is involved in a number of patent litigation lawsuits involving the validity and/or infringement of patents held by branded pharmaceutical manufacturers including but not limited to the matters described below. The Company uses its business judgement to decide to market and sell certain products, in each case based on its belief that the applicable patents are invalid and/or that its products do not infringe, notwithstanding the fact that allegations of patent infringement(s) or other potential third party rights have not been finally resolved by the courts." (*Id.*) Following this statement, Viatris Inc. identifies multiple Hatch-Waxman litigations in which Mylan Pharmaceuticals Inc. is involved. (*Id.*)

61. On information and belief, Mylan Pharmaceuticals Inc. acting as an alter ego of Viatris Inc. develops, manufactures, distributes, sells and/or imports drug products for the entire United States market and does business in every state including Delaware, either directly or indirectly.

62. On information and belief, Mylan Laboratories Limited develops, manufactures, distributes, sells, and/or imports drug products for the entire United States market and does business in every state including Delaware, either directly or indirectly.

63. On information and belief, including, based on, *inter alia*, the Mylan Defendants' website, publicly-available SEC 10-K filings, and publicly-available press releases, the Mylan Defendants hold themselves out as a unitary entity and operate as a single integrated business with respect to the regulatory approval, manufacturing, marketing, sale and distribution of generic pharmaceutical products throughout the United States, including Delaware.

64. On information and belief, the Mylan Defendants act in concert, with Mylan Pharmaceuticals Inc. and Viatris acting as a single enterprise, with respect to the preparation,

submission, approval and maintenance of ANDAs, including ANDAs as filed and amendments thereto. On information and belief, Mylan Pharmaceuticals Inc., acting as an alter ego of Viatris Inc., has submitted to the FDA ANDA No. 213646 for sacubitril/valsartan tablets, 24 mg/26 mg, 49 mg/51 mg, and 97 mg/103 mg ("Mylan ANDA Products"), including amendments seeking FDA approval to engage in the commercial manufacture, use, sale, offer for sale, and/or importation of the Mylan ANDA Products in or into the United States, including Delaware, prior to the expiration of the '918 patent.

65. Mylan Pharmaceuticals Inc., acting as an alter ego of Viatris Inc., has committed an act of infringement in this judicial district by filing ANDA No. 213646, including amendments, with the intent to make, use, sell, offer for sale, and/or import the Mylan ANDA Products in or into this judicial district, prior to the expiration of the '918 patent, an act of infringement that has led and will lead to foreseeable harm and injury to Novartis.

66. On information and belief, the Mylan Defendants acted in concert, with Mylan Pharmaceuticals Inc. and Viatris Inc. acting as a single enterprise, in the preparation and submission of ANDA No. 213646, including amendments, and, if the ANDA is approved, will continue to act in concert, with Mylan Pharmaceuticals Inc. and Viatris Inc. acting as a single enterprise, to engage in the commercial manufacture, use, sale, offer for sale, and/or importation of the Mylan ANDA Products in or into the United States, including Delaware, prior to the expiration of the '918 patent.

67. The Mylan Defendants, acting in concert, with Mylan Pharmaceuticals Inc. and Viatris Inc. acting as a single enterprise, have taken the costly, significant step of applying to the FDA for approval, including submission of ANDA No. 213646 as filed and amendments thereto,

to engage in future activities, including the marketing of the Mylan ANDA Products, that will be purposefully directed at Delaware and elsewhere.

68. On information and belief, Mylan Pharmaceuticals Inc., acting as an alter ego of Viatris Inc., has systematic and continuous contacts with Delaware; has established distribution channels for drug products in Delaware; regularly and continuously conducts business in Delaware, including by selling drug products in Delaware, either directly or indirectly through its subsidiaries, agents, or affiliates; has purposefully availed itself of the privilege of doing business in Delaware; and derives substantial revenue from the sale of drug products in Delaware.

69. On information and belief, Mylan Laboratories Limited has systematic and continuous contacts with Delaware, has established distribution channels for drug products in Delaware, regularly and continuously conducts business in Delaware, including by selling drug products in Delaware, either directly or indirectly through its subsidiaries, agents, or affiliates; has purposefully availed itself of the privilege of doing business in Delaware; and derives substantial revenue from the sale of drug products in Delaware.

70. On information and belief, Viatris Inc. has systematic and continuous contacts with Delaware; has established distribution channels for drug products in Delaware; regularly and continuously conducts business in Delaware, including by selling drug products in Delaware, either directly or indirectly through its subsidiaries, agents, or affiliates; has purposefully availed itself of the privilege of doing business in Delaware; and derives substantial revenue from the sale of drug products in Delaware.

e. Nanjing Noratech Pharmaceutical Co., Limited (ANDA No. 213671)

71. On information and belief, Nanjing Noratech Pharmaceutical Co., Limited ("Noratech") is a corporation organized and existing under the laws of China, having a principal place of business at 6/F, Building F6, No. 9 Weidi Road, Jiangsu Life Science and Technology Innovation Park, Qixia District, Nanjing, China.

72. On information and belief, Noratech develops, manufactures, distributes, sells, and/or imports drug products for the entire United States market and does business in every state including Delaware, either directly or indirectly.

73. On information and belief, Noratech has submitted to the FDA ANDA No. 213671 for sacubitril/valsartan tablets, 24 mg/26 mg, 49 mg/51 mg, and 97 mg/103 mg ("Noratech ANDA Products"), seeking FDA approval to engage in the commercial manufacture, use, sale, offer for sale, and/or importation of the Noratech ANDA Products in or into the United States, including Delaware, prior to the expiration of the '918 patent.

74. Noratech has committed an act of infringement in this judicial district by filing ANDA No. 213671 with the intent to make, use, sell, offer for sale, and/or import the Noratech ANDA Products in or into this judicial district, prior to the expiration of the '918 patent, an act of infringement that has led and will lead to foreseeable harm and injury to Novartis, a Delaware corporation.

75. Noratech has taken the costly, significant step of applying to the FDA for approval to engage in future activities, including the marketing of the Noratech ANDA Products, that will be purposefully directed at Delaware and elsewhere.

76. On information and belief, Noratech has systematic and continuous contacts with Delaware; has established distribution channels for drug products in Delaware; regularly and

continuously conducts business in Delaware, including by selling drug products in Delaware, either directly or indirectly through its subsidiaries, agents, or affiliates; has purposefully availed itself of the privilege of doing business in Delaware; and derives substantial revenue from the sale of drug products in Delaware.

77. Noratech, the entity that, on information and belief, submitted ANDA No. 213671, has agreed with Novartis to litigate any patent action(s) concerning ANDA No. 213671 in the District of Delaware, and has agreed, only for the purposes of such action(s), not to challenge personal jurisdiction and venue in the District of Delaware.

JURISDICTION AND VENUE

78. This Court has jurisdiction over the subject matter of this action under 28 U.S.C. §§ 1331, 1338(a), 2201, and 2202.

a. Alembic Pharmaceuticals Limited; Alembic Global Holding SA; Alembic Pharmaceuticals, Inc.
(ANDA No. 213682)

79. This Court has personal jurisdiction over Alembic Pharmaceuticals Limited, Alembic Global Holding SA, and Alembic Pharmaceuticals, Inc. because, on information and belief, each such Defendant has committed or has aided, abetted, contributed to, or participated in the commission of tortious acts of patent infringement in preparing and submitting ANDA No. 213682 with a certification pursuant to 21 U.S.C. § 355(j)(2)(A)(vii)(IV), which acts have led to foreseeable harm and injury to Novartis, a Delaware corporation.

80. This Court also has personal jurisdiction over Alembic Pharmaceuticals Limited, Alembic Global Holding SA, and Alembic Pharmaceuticals, Inc. because, on information and belief, each such Defendant, upon approval of ANDA No. 213682, will commit or will aid, abet, contribute to, or participate in future tortious acts of patent infringement permitted under ANDA

No. 213682 that will be purposefully directed at Delaware, including the marketing of the Alembic ANDA Products in Delaware, prior to the expiration of the '918 patent.

81. This Court also has personal jurisdiction over Alembic Pharmaceuticals Limited, Alembic Global Holding SA, and Alembic Pharmaceuticals, Inc. because, on information and belief, each such Defendant's affiliations with the State of Delaware, including Alembic Pharmaceuticals, Inc.'s incorporation in Delaware, and Alembic Pharmaceuticals Limited's and Alembic Global Holding SA's ownership of and actions in concert with Alembic Pharmaceuticals, Inc., are sufficiently continuous and systematic as to render each such Defendant essentially at home in this forum.

82. This Court also has personal jurisdiction over Alembic Pharmaceuticals Limited, Alembic Global Holding SA, and Alembic Pharmaceuticals, Inc. because each such Defendant has availed itself of the legal protections of the State of Delaware, by admitting jurisdiction and asserting counterclaims in lawsuits filed in the United States District Court for the District of Delaware.

83. Alembic Pharmaceuticals Limited, the entity that, on information and belief, submitted ANDA No. 213682, has agreed with Novartis to litigate any patent action(s) concerning ANDA No. 213682 in the District of Delaware, and has agreed, only for the purposes of such action(s), not to challenge personal jurisdiction and venue in the District of Delaware.

84. For these reasons, and for other reasons that will be presented to the Court if jurisdiction is challenged, the Court has personal jurisdiction over Alembic Pharmaceuticals Limited, Alembic Global Holding SA, and Alembic Pharmaceuticals, Inc.

85. Venue is proper in this Court because Alembic Pharmaceuticals, Inc. is incorporated in the State of Delaware and therefore resides in this judicial district, and because

Alembic Pharmaceuticals Limited and Alembic Global Holding SA are foreign entities who may be sued in any judicial district, including Delaware. 28 U.S.C. § 1400(b); 28 U.S.C. § 1391(c)(3).

b. Crystal Pharmaceutical (Suzhou) Co., Ltd. (ANDA No. 213605)

86. This Court has personal jurisdiction over Crystal because Crystal has committed tortious acts of patent infringement in preparing and submitting ANDA No. 213605 with a certification pursuant to 21 U.S.C. § 355(j)(2)(A)(vii)(IV), which acts have led to foreseeable harm and injury to Plaintiff Novartis, a Delaware corporation.

87. This Court also has personal jurisdiction over Crystal because, on information and belief, Crystal, upon approval of ANDA No. 213605, will commit or will aid, abet, contribute to, or participate in future tortious acts of patent infringement permitted under ANDA No. 213605 that will be purposefully directed at Delaware, including the marketing of the Crystal ANDA Products in Delaware, prior to the expiration of the '918 patent.

88. This Court also has personal jurisdiction over Crystal because, on information and belief, Crystal's affiliations with the State of Delaware are sufficiently continuous and systematic as to render Crystal essentially at home in this forum.

89. Crystal, the entity that, on information and belief, submitted ANDA No. 213605, has agreed with Novartis to litigate any patent action(s) concerning ANDA No. 213605 in the District of Delaware and not to contest personal jurisdiction or venue in the District of Delaware in such an action.

90. For these reasons, and for other reasons that will be presented to the Court if jurisdiction is challenged, the Court has personal jurisdiction over Crystal.

91. Venue is proper in this Court because Crystal is a foreign entity who may be sued in any judicial district, including the District of Delaware. 28 U.S.C. § 1391(c)(3).

c. MSN Pharmaceuticals Inc.; MSN Laboratories Private Limited; MSN Life Sciences Private Limited (ANDA No. 213748)

92. This Court has personal jurisdiction over MSN Pharmaceuticals Inc., MSN Laboratories Private Limited, and MSN Life Sciences Private Limited because, on information and belief, each such Defendant has committed or has aided, abetted, contributed to, or participated in the commission of tortious acts of patent infringement in preparing and submitting ANDA No. 213748 with a certification pursuant to 21 U.S.C. § 355(j)(2)(A)(vii)(IV), which acts have led to foreseeable harm and injury to Novartis, a Delaware corporation.

93. This Court also has personal jurisdiction over MSN Pharmaceuticals Inc., MSN Laboratories Private Limited, and MSN Life Sciences Private Limited because, on information and belief, each such Defendant, upon approval of ANDA No. 213748, will commit or will aid, abet, contribute to, or participate in future tortious acts of patent infringement permitted under ANDA No. 213748 that will be purposefully directed at Delaware, including the marketing of the MSN ANDA Products in Delaware, prior to the expiration of the '918 patent.

94. This Court also has personal jurisdiction over MSN Pharmaceuticals Inc., MSN Laboratories Private Limited, and MSN Life Sciences Private Limited because each such Defendant's affiliations with the State of Delaware, including MSN Pharmaceuticals Inc.'s incorporation in Delaware, MSN Laboratories Private Limited's ownership of and actions in concert with MSN Pharmaceuticals Inc., and MSN Life Sciences Private Limited's actions in concert with MSN Pharmaceuticals Inc. are sufficiently continuous and systematic as to render each such Defendant essentially at home in this forum.

95. This Court also has personal jurisdiction over MSN Pharmaceuticals Inc. and MSN Laboratories Private Limited because each such Defendant has availed itself of the legal

protections of the State of Delaware, by admitting jurisdiction and asserting counterclaims in lawsuits filed in the United States District Court for the District of Delaware.

96. MSN Pharmaceuticals Inc. and MSN Laboratories Private Limited, the entities that, on information and belief, submitted ANDA No. 213748, have agreed with Novartis to litigate any patent action(s) concerning ANDA No. 213748 in the District of Delaware, and have agreed, only for the purposes of such action(s), not to challenge personal jurisdiction and venue in the District of Delaware.

97. For these reasons, and for other reasons that will be presented to the Court if jurisdiction is challenged, the Court has personal jurisdiction over MSN Pharmaceuticals Inc., MSN Laboratories Private Limited, and MSN Life Sciences Private Limited.

98. Venue is proper in this Court because MSN Pharmaceuticals Inc. is incorporated in the State of Delaware and therefore resides in this judicial district, and because MSN Laboratories Private Limited and MSN Life Sciences Private Limited are foreign entities who may be sued in any judicial district, including Delaware. 28 U.S.C. § 1400(b); 28 U.S.C. § 1391(c)(3).

d. Mylan Pharmaceuticals Inc.; Mylan Laboratories Limited; Viatris Inc. (collectively, the "Mylan Defendants") (ANDA No. 213646)

99. This Court has personal jurisdiction over the Mylan Defendants because, on information and belief, the Mylan Defendants, acting in concert, with Mylan Pharmaceuticals Inc. and Viatris Inc. acting as a single enterprise, have committed and/or have aided, abetted, contributed to, or participated in the commission of tortious acts of patent infringement in preparing and submitting ANDA No. 213646 with a certification pursuant to 21 U.S.C. §

355(j)(2)(A)(vii)(IV), including its amendments, which acts have led to foreseeable harm and injury to Novartis, a Delaware corporation.

100. This Court also has personal jurisdiction over the Mylan Defendants because, on information and belief, the Mylan Defendants, acting in concert, with Mylan Pharmaceuticals Inc. and Viatris Inc. acting as a single enterprise, upon approval of ANDA No. 213646, will commit or will aid, abet, contribute to, or participate in future tortious acts of patent infringement permitted under ANDA No. 213646 that will be purposefully directed at Delaware, including the marketing of the Mylan ANDA Products in Delaware, prior to the expiration of the '918 patent.

101. This Court also has personal jurisdiction over the Mylan Defendants because, on information and belief, each such Defendant's affiliations with the State of Delaware, including Viatris Inc.'s incorporation in Delaware, Viatris Inc.'s ownership of and actions in concert and as a single enterprise with Mylan Pharmaceuticals Inc., Viatris Inc.'s ownership of and actions in concert with Mylan Laboratories Limited, are sufficiently continuous and systematic as to render each such Defendant essentially at home in this forum.

102. On information and belief, it would be unfair not to impute Viatris Inc.'s residency to Mylan Pharmaceuticals Inc. as the alter ego of Viatris Inc. when Viatris Inc. has so dominated and subsumed Mylan Pharmaceuticals Inc. into Viatris Inc.

103. Venue is proper in this Court because Viatris Inc. is incorporated in the State of Delaware and therefore resides in this judicial district, because Viatris Inc.'s Delaware residence should be imputed to Mylan Pharmaceuticals Inc. as an alter ego of Viatris Inc. due to a lack of corporate separateness between Viatris Inc. and Mylan Pharmaceuticals Inc., and because Mylan Laboratories Limited is a foreign entity who may be sued in any judicial district, including the District of Delaware. 28 U.S.C. § 1391(c)(3).

104. For these reasons and for other reasons that will be presented to the Court if jurisdiction or venue is challenged, the Court has personal jurisdiction over Mylan Pharmaceuticals Inc., and Viatris Inc., and venue is proper in this judicial district.

e. Nanjing Noratech Pharmaceutical Co., Limited (ANDA No. 213671)

105. This Court has personal jurisdiction over Noratech because Noratech has committed tortious acts of patent infringement in preparing and submitting ANDA No. 213671 with a certification pursuant to 21 U.S.C. § 355(j)(2)(A)(vii)(IV), which acts have led to foreseeable harm and injury to Novartis, a Delaware corporation.

106. This Court also has personal jurisdiction over Noratech because, on information and belief, Noratech, upon approval of ANDA No. 213671, will commit or will aid, abet, contribute to, or participate in future tortious acts of patent infringement permitted under ANDA No. 213671 that will be purposefully directed at Delaware, including the marketing of the Noratech ANDA Products in Delaware, prior to the expiration of the '918 patent.

107. This Court also has personal jurisdiction over Noratech because, on information and belief, Noratech's affiliations with the State of Delaware are sufficiently continuous and systematic as to render Noratech essentially at home in this forum.

108. Noratech, the entity that, on information and belief, submitted ANDA No. 213671, has agreed with Novartis to litigate any patent action(s) concerning ANDA No. 213671 in the District of Delaware, and has agreed, only for the purposes of such action(s), not to challenge personal jurisdiction and venue in the District of Delaware.

109. For these reasons, and for other reasons that will be presented to the Court if jurisdiction is challenged, the Court has personal jurisdiction over Noratech.

110. Venue is proper in this Court because Noratech is a foreign entity who may be sued in any judicial district, including Delaware. 28 U.S.C. § 1391(c)(3).

THE PATENT-IN-SUIT AND ENTRESTO®

111. Novartis is the owner of the '918 patent, titled "Amorphous solid form of compounds containing S-N-valeryl-N-{[2′-(1H-tetrazole-5-yl)-biphenyl-4-yl]-methyl}-valine and (2R,4S)-5-biphenyl-4-yl-4-(3-carboxy-propionylamino)-2-methyl-pentanoic acid ethyl ester moieties and sodium cations." The '918 patent was duly and legally issued on August 24, 2021. A true and correct copy of the '918 patent is attached hereto as Exhibit A.

112. The '918 patent claims, *inter alia*, an amorphous solid form of a compound comprising anionic valsartan, anionic sacubitril, and sodium cations in a 1:1:3 molar ratio.

113. Novartis is the holder of New Drug Application ("NDA") No. 207620 by which the FDA granted approval for the commercial manufacturing, marketing, sale, and use of ENTRESTO® (sacubitril and valsartan) tablets, 24 mg/26 mg, 49 mg/51 mg, and 97 mg/103 mg. ENTRESTO® currently is indicated to reduce the risk of cardiovascular death and hospitalization for heart failure in adult patients with chronic heart failure, and for the treatment of symptomatic heart failure with systemic left ventricular systolic dysfunction in pediatric patients aged one year and older.

INFRINGEMENT BY EACH DEFENDANT OF THE PATENT-IN-SUIT

114. Novartis incorporates paragraphs 1 – 113 as if fully set forth herein.

a. Alembic Pharmaceuticals Limited; Alembic Global Holding SA; Alembic Pharmaceuticals, Inc.
(ANDA No. 213682)

115. On information and belief, Alembic Pharmaceuticals Limited, by itself or in concert with Alembic Global Holding SA, and/or Alembic Pharmaceuticals, Inc., submitted to the FDA ANDA No. 213682 under the provisions of 21 U.S.C. § 355(j) seeking approval to

engage in the commercial manufacture, use, sale, offer for sale, and/or importation of the Alembic ANDA Products prior to the expiration of the '918 patent.

116. By filing its ANDA under 21 U.S.C. § 355(j) for the purpose of obtaining approval to engage in the commercial manufacture, use, sale, offer for sale, and/or importation of the Alembic ANDA Products in or into the United States prior to the expiration of the '918 patent, Alembic Pharmaceuticals Limited, and, on information and belief, Alembic Global Holding SA, and Alembic Pharmaceuticals, Inc., have committed an act of infringement under 35 U.S.C. § 271(e)(2).

117. On information and belief, the commercial manufacture, use, sale, offer for sale, and/or importation of the Alembic ANDA Products in or into the United States will directly infringe one or more claims of the '918 patent.

118. On information and belief, the Alembic ANDA Products are a pharmaceutical composition in the form of a tablet comprising an amorphous solid form of a compound comprising (i) anionic valsartan, (ii) anionic sacubitril, and (iii) sodium cations in a 1:1:3 molar ratio. On information and belief, the commercial manufacture, use, sale, offer for sale, and/or importation of the Alembic ANDA Products in or into the United States will directly infringe one or more claims of the '918 patent.

119. Novartis will be substantially and irreparably damaged by Alembic Pharmaceuticals Limited's, Alembic Global Holding SA's, and/or Alembic Pharmaceuticals, Inc.'s infringement of the '918 patent.

120. Novartis is entitled to the relief provided by 35 U.S.C. § 271(e)(4) and 35 U.S.C. § 283, including an order of this Court that the effective date of any approval of ANDA No. 213682 be a date that is no earlier than November 8, 2026, the expiration of the '918 patent, or a

date no earlier than the expiry of any other patent extension or exclusivity to which Novartis is entitled, and an award of damages for any commercial sale or use of the Alembic ANDA Products and any act committed by Alembic Pharmaceuticals Limited, Alembic Global Holding SA, and/or Alembic Pharmaceuticals, Inc. with respect to the subject matter claimed in the '918 patent, which act is not within the limited exclusions of 35 U.S.C. § 271(e)(1).

121. On information and belief, Alembic Pharmaceuticals Limited, Alembic Global Holding SA, and/or Alembic Pharmaceuticals, Inc. have taken and continue to take active steps towards the commercial manufacture, use, sale, offer for sale, and/or importation of the Alembic ANDA Products, including seeking approval of those products under ANDA No. 213682.

122. There is a substantial and immediate controversy between Novartis and Alembic Pharmaceuticals Limited, Alembic Global Holding SA, and Alembic Pharmaceuticals, Inc. concerning the '918 patent. Novartis is entitled to declaratory judgment under 28 U.S.C. §§ 2201 and 2202 that Alembic will directly infringe one or more claims of the '918 patent.

b. Crystal Pharmaceutical (Suzhou) Co., Ltd. (ANDA No. 213605)

123. On information and belief, Crystal submitted to the FDA ANDA No. 213605 under the provisions of 21 U.S.C. § 355(j) seeking approval to engage in the commercial manufacture, use, sale, offer for sale, and/or importation of the Crystal ANDA Products prior to the expiration of the '918 patent.

124. By filing its ANDA under 21 U.S.C. § 355(j) for the purpose of obtaining approval to engage in the commercial manufacture, use, sale, offer for sale, and/or importation of the Crystal ANDA Products in or into the United States prior to the expiration of the '918 patent, Crystal has committed an act of infringement under 35 U.S.C. § 271(e)(2).

125. On information and belief, the commercial manufacture, use, sale, offer for sale, and/or importation of the Crystal ANDA Products in or into the United States will directly infringe one or more claims of the '918 patent.

126. On information and belief, the Crystal ANDA Products are a pharmaceutical composition in the form of a tablet comprising (in an amount less than 10% by weight of the total amount of active ingredient in the tablet) an amorphous solid form of a compound comprising (i) anionic valsartan, (ii) anionic sacubitril, and (iii) sodium cations in a 1:1:3 molar ratio. On information and belief, the commercial manufacture, use, sale, offer for sale, and/or importation of the Crystal ANDA Products in or into the United States will directly infringe one or more claims of the '918 patent.

127. Novartis will be substantially and irreparably damaged by Crystal's infringement of the '918 patent.

128. Novartis is entitled to the relief provided by 35 U.S.C. § 271(e)(4) and 35 U.S.C. § 283, including an order of this Court that the effective date of any approval of ANDA No. 213605 be a date that is no earlier than November 8, 2026, the expiration of the '918 patent, or a date no earlier than the expiry of any other patent extension or exclusivity to which Novartis is entitled, and an award of damages for any commercial sale or use of the Crystal ANDA Products and any act committed by Crystal with respect to the subject matter claimed in the '918 patent, which act is not within the limited exclusions of 35 U.S.C. § 271(e)(1).

129. On information and belief, Crystal has taken and continues to take active steps towards the commercial manufacture, use, sale, offer for sale, and/or importation of the Crystal ANDA Products, including seeking approval of those products under ANDA No. 213605.

130. There is a substantial and immediate controversy between Novartis and Crystal concerning the '918 patent. Novartis is entitled to declaratory judgment under 28 U.S.C. §§ 2201 and 2202 that Crystal will directly infringe one or more claims of the '918 patent.

c. MSN Pharmaceuticals Inc.; MSN Laboratories Private Limited; MSN Life Sciences Private Limited (ANDA No. 213748)

131. On information and belief, MSN Pharmaceuticals Inc. and MSN Laboratories Private Limited, by themselves or in concert with MSN Life Sciences Private Limited, submitted to the FDA ANDA No. 213748 under the provisions of 21 U.S.C.§ 355(j) seeking approval to engage in the commercial manufacture, use, sale, offer for sale, and/or importation of the MSN ANDA Products prior to the expiration of the '918 patent.

132. By filing their ANDA under 21 U.S.C. § 355(j) for the purpose of obtaining approval to engage in the commercial manufacture, use, sale, offer for sale, and/or importation of the MSN ANDA Products in or into the United States prior to the expiration of the '918 patent, MSN Pharmaceuticals Inc. and MSN Laboratories Private Limited, and on information and belief, MSN Life Sciences Private Limited, have committed an act of infringement under 35 U.S.C. § 271(e)(2).

133. On information and belief, the commercial manufacture, use, sale, offer for sale, and/or importation of the MSN ANDA Products in or into the United States will directly infringe one or more claims of the '918 patent.

134. On information and belief, the MSN ANDA Products are a pharmaceutical composition in the form of a tablet comprising an amorphous solid form of a compound comprising (i) anionic valsartan, (ii) anionic sacubitril, and (iii) sodium cations in a 1:1:3 molar ratio. On information and belief, the commercial manufacture, use, sale, offer for sale, and/or

importation of the MSN ANDA Products in or into the United States will directly infringe one or more claims of the '918 patent.

135. Novartis will be substantially and irreparably damaged by MSN Pharmaceuticals Inc.'s, MSN Laboratories Private Limited's, and MSN Life Sciences Private Limited's infringement of the '918 patent.

136. Novartis is entitled to the relief provided by 35 U.S.C. § 271(e)(4) and 35 U.S.C. § 283, including an order of this Court that the effective date of any approval of ANDA No. 213748 be a date that is no earlier than November 8, 2026, the expiration of the '918 patent, or a date no earlier than the expiry of any other patent extension or exclusivity to which Novartis is entitled, and an award of damages for any commercial sale or use of the MSN ANDA Products and any act committed by MSN Pharmaceuticals Inc., MSN Laboratories Private Limited, and MSN Life Sciences Private Limited with respect to the subject matter claimed in the '918 patent, which act is not within the limited exclusions of 35 U.S.C. § 271(e)(1).

137. On information and belief, MSN Pharmaceuticals Inc., MSN Laboratories Private Limited, and MSN Life Sciences Private Limited have taken and continue to take active steps towards the commercial manufacture, use, sale, offer for sale, and/or importation of the MSN ANDA Products, including seeking approval of those products under ANDA No. 213748.

138. There is a substantial and immediate controversy between Novartis and MSN Pharmaceuticals Inc., MSN Laboratories Private Limited, and MSN Life Sciences Private Limited concerning the '918 patent. Novartis is entitled to declaratory judgment under 28 U.S.C. §§ 2201 and 2202 that MSN Pharmaceuticals Inc., MSN Laboratories Private Limited, and MSN Life Sciences Private Limited will directly infringe one or more claims of the '918 patent.

d. Mylan Pharmaceuticals Inc.; Mylan Laboratories Limited; Viatris Inc. (collectively, the "Mylan Defendants") (ANDA No. 213646)

139. On information and belief, Mylan Pharmaceuticals Inc., acting in concert and as a single enterprise with Viatris Inc. and acting in concert with Mylan Laboratories Limited submitted to the FDA ANDA No. 213646 under the provisions of 21 U.S.C. § 355(j), including its amendments, seeking approval to engage in the commercial manufacture, use, sale, offer for sale, and/or importation of the Mylan ANDA Products prior to the expiration of the '918 patent.

140. By filing their ANDA under 21 U.S.C. § 355(j) for the purpose of obtaining approval to engage in the commercial manufacture, use, sale, offer for sale, and/or importation of the Mylan ANDA Products in or into the United States prior to the expiration of the '918 patent, Mylan Pharmaceuticals Inc. and, on information and belief, acting in concert and as a single enterprise with Viatris Inc., and acting in concert with Mylan Laboratories Limited have committed an act of infringement under 35 U.S.C. § 271(e)(2).

141. On information and belief, the commercial manufacture, use, sale, offer for sale, and/or importation of the Mylan ANDA Products in or into the United States will directly infringe one or more claims of the '918 patent.

142. On information and belief, the Mylan ANDA Products are a pharmaceutical composition in the form of a tablet comprising (in an amount less than 10% by weight of the total amount of active ingredient in the tablet) an amorphous solid form of a compound comprising (i) anionic valsartan, (ii) anionic sacubitril, and (iii) sodium cations in a 1:1:3 molar ratio. On information and belief, the commercial manufacture, use, sale, offer for sale, and/or importation of the Mylan ANDA Products in or into the United States will directly infringe one or more claims of the '918 patent.

143. Novartis will be substantially and irreparably damaged by the Mylan Defendants' infringement of the '918 patent.

144. Novartis is entitled to the relief provided by 35 U.S.C. § 271(e)(4) and 35 U.S.C. § 283, including an order of this Court that the effective date of any approval of ANDA No. 213646 be a date that is no earlier than November 8, 2026, the expiration of the '918 patent, or a date no earlier than the expiry of any other patent extension or exclusivity to which Novartis is entitled, and an award of damages for any commercial sale or use of the Mylan ANDA Products and any act committed by the Mylan Defendants with respect to the subject matter claimed in the '918 patent, which act is not within the limited exclusions of 35 U.S.C. § 271(e)(1).

145. On information and belief, Mylan Pharmaceuticals Inc., acting in concert and as a single enterprise with Viatris Inc. and acting in concert with Mylan Laboratories Limited have taken and continue to take active steps towards the commercial manufacture, use, sale, offer for sale, and/or importation of the Mylan ANDA Products, including seeking approval of those products under ANDA No. 213646.

146. There is a substantial and immediate controversy between Novartis and the Mylan Defendants concerning the '918 patent. Novartis is entitled to declaratory judgment under 28 U.S.C. §§ 2201 and 2202 that Mylan Pharmaceuticals Inc., acting in concert and as a single enterprise with Viatris Inc. and acting in concert with Mylan Laboratories Limited will directly infringe one or more claims of the '918 patent.

e. Nanjing Noratech Pharmaceutical Co., Limited (ANDA No. 213671)

147. On information and belief, Noratech submitted to the FDA ANDA No. 213671 under the provisions of 21 U.S.C. § 355(j) seeking approval to engage in the commercial

manufacture, use, sale, offer for sale, and/or importation of the Noratech ANDA Products prior to the expiration of the '918 patent.

148. By filing its ANDA under 21 U.S.C. § 355(j) for the purpose of obtaining approval to engage in the commercial manufacture, use, sale, offer for sale, and/or importation of the Noratech ANDA Products in or into the United States prior to the expiration of the '918 patent, Noratech has committed an act of infringement under 35 U.S.C. § 271(e)(2).

149. On information and belief, the commercial manufacture, use, sale, offer for sale, and/or importation of the Noratech ANDA Products in or into the United States will directly infringe one or more claims of the '918 patent.

150. On information and belief, the Noratech ANDA Products are a pharmaceutical composition in the form of a tablet comprising an amorphous solid form of a compound comprising (i) anionic valsartan, (ii) anionic sacubitril, and (iii) sodium cations in a 1:1:3 molar ratio. On information and belief, the commercial manufacture, use, sale, offer for sale, and/or importation of the Noratech ANDA Products in or into the United States will directly infringe one or more claims of the '918 patent.

151. Novartis will be substantially and irreparably damaged by Noratech's infringement of the '918 patent.

152. Novartis is entitled to the relief provided by 35 U.S.C. § 271(e)(4) and 35 U.S.C. § 283, including an order of this Court that the effective date of any approval of ANDA No. 213671 be a date that is no earlier than November 8, 2026, the expiration of the '918 patent, or a date no earlier than the expiry of any other patent extension or exclusivity to which Novartis is entitled, and an award of damages for any commercial sale or use of the Noratech ANDA

Products and any act committed by Noratech with respect to the subject matter claimed in the '918 patent, which act is not within the limited exclusions of 35 U.S.C. § 271(e)(1).

153. On information and belief, Noratech has taken and continues to take active steps towards the commercial manufacture, use, sale, offer for sale, and/or importation of the Noratech ANDA Products, including seeking approval of those products under ANDA No. 213671.

154. There is a substantial and immediate controversy between Novartis and Noratech concerning the '918 patent. Novartis is entitled to declaratory judgment under 28 U.S.C. §§ 2201 and 2202 that Noratech will directly infringe one or more claims of the '918 patent.

PRAYER FOR RELIEF

WHEREFORE, Novartis prays that this Court grant the following relief:

a. Alembic Pharmaceuticals Limited; Alembic Global Holding SA; Alembic Pharmaceuticals, Inc. (ANDA No. 213682)

155. Judgment that Defendants Alembic Pharmaceuticals Limited, Alembic Global Holding SA, and Alembic Pharmaceuticals, Inc. have infringed one or more claims of the '918 patent by filing ANDA No. 213682;

156. A permanent injunction restraining and enjoining Defendants Alembic Pharmaceuticals Limited, Alembic Global Holding SA, and Alembic Pharmaceuticals, Inc. and their officers, agents, attorneys, and employees, and those acting in privity or concert with them, from engaging in the commercial manufacture, use, sale, or offer for sale in the United States, or importation into the United States, of the Alembic ANDA Products prior to the expiration of the '918 patent, inclusive of any extensions and additional periods of exclusivity;

157. An order that the effective date of any approval of ANDA No. 213682 be a date that is not earlier than the expiration date of the '918 patent, inclusive of any extensions and additional periods of exclusivity;

158. Declaratory judgment that the commercial manufacture, use, sale, offer for sale, and/or importation of the Alembic ANDA Products will directly infringe one or more claims of the '918 patent;

159. Damages or other monetary relief from Defendants Alembic Pharmaceuticals Limited, Alembic Global Holding SA, and Alembic Pharmaceuticals, Inc. for the direct infringement of the '918 patent;

160. A declaration that this case is an exceptional case pursuant to 35 U.S.C. § 285 and an award of attorney's fees;

161. Novartis's costs and expenses in this action; and

162. Such other and further relief as the Court may deem just and proper.

b. Crystal Pharmaceutical (Suzhou) Co., Ltd. (ANDA No. 213605)

163. Judgment that Defendant Crystal has infringed one or more claims of the '918 patent by filing ANDA No. 213605;

164. A permanent injunction restraining and enjoining Defendant Crystal and its officers, agents, attorneys, and employees, and those acting in privity or concert with them, from engaging in the commercial manufacture, use, sale, or offer for sale in the United States, or importation into the United States, of the Crystal ANDA Products prior to the expiration of the '918 patent, inclusive of any extensions and additional periods of exclusivity;

165. An order that the effective date of any approval of ANDA No. 213605 be a date that is not earlier than the expiration date of the '918 patent, inclusive of any extensions and additional periods of exclusivity;

166. Declaratory judgment that the commercial manufacture, use, sale, offer for sale, and/or importation of the Crystal ANDA Products will directly infringe one or more claims of the '918 patent;

167. Damages or other monetary relief from Defendant Crystal for the direct infringement of the '918 patent;

168. A declaration that this case is an exceptional case pursuant to 35 U.S.C. § 285 and an award of attorney's fees;

169. Novartis's costs and expenses in this action; and

170. Such other and further relief as the Court may deem just and proper.

c. MSN Pharmaceuticals Inc.; MSN Laboratories Private Limited; MSN Life Sciences Private Limited (ANDA No. 213748)

171. Judgment that Defendants MSN Pharmaceuticals Inc., MSN Laboratories Private Limited, and MSN Life Sciences Private Limited have infringed one or more claims of the '918 patent by filing ANDA No. 213748;

172. A permanent injunction restraining and enjoining Defendants MSN Pharmaceuticals Inc., MSN Laboratories Private Limited, and MSN Life Sciences Private Limited and their officers, agents, attorneys, and employees, and those acting in privity or concert with them, from engaging in the commercial manufacture, use, sale, or offer for sale in the United States, or importation into the United States, of the MSN ANDA Products prior to the expiration of the '918 patent, inclusive of any extensions and additional periods of exclusivity;

173. An order that the effective date of any approval of ANDA No. 213748 be a date that is not earlier than the expiration date of the '918 patent, inclusive of any extensions and additional periods of exclusivity;

174. Declaratory judgment that the commercial manufacture, use, sale, offer for sale, and/or importation of the MSN ANDA Products will directly infringe one or more claims of the '918 patent;

175. Damages or other monetary relief from Defendants MSN Pharmaceuticals Inc., MSN Laboratories Private Limited, and MSN Life Sciences Private Limited for the direct infringement of the '918 patent;

176. A declaration that this case is an exceptional case pursuant to 35 U.S.C. § 285 and an award of attorney's fees;

177. Novartis's costs and expenses in this action; and

178. Such other and further relief as the Court may deem just and proper.

d. Mylan Pharmaceuticals Inc.; Mylan Laboratories Limited; Viatris Inc. (collectively, the "Mylan Defendants") (ANDA No. 213646)

179. Judgment that the Mylan Defendants have infringed one or more claims of the '918 patent by filing ANDA No. 213646;

180. A permanent injunction restraining and enjoining the Mylan Defendants and their officers, agents, attorneys, and employees, and those acting in privity or concert with them, from engaging in the commercial manufacture, use, sale, or offer for sale in the United States, or importation into the United States, of the Mylan ANDA Products prior to the expiration of the '918 patent, inclusive of any extensions and additional periods of exclusivity;

181. An order that the effective date of any approval of ANDA No. 213646 be a date that is not earlier than the expiration date of the '918 patent, inclusive of any extensions and additional periods of exclusivity;

182. Declaratory judgment that the commercial manufacture, use, sale, offer for sale, and/or importation of the Mylan ANDA Products will directly infringe one or more claims of the '918 patent;

183. Damages or other monetary relief from the Mylan Defendants for the direct infringement of the '918 patent;

184. A declaration that this case is an exceptional case pursuant to 35 U.S.C. § 285 and an award of attorney's fees;

185. Novartis's costs and expenses in this action; and

186. Such other and further relief as the Court may deem just and proper.

e. Nanjing Noratech Pharmaceutical Co., Limited (ANDA No. 213671)

187. Judgment that Defendant Noratech has infringed one or more claims of the '918 patent by filing ANDA No. 213671;

188. A permanent injunction restraining and enjoining Defendant Noratech, and its officers, agents, attorneys, and employees, and those acting in privity or concert with them, from engaging in the commercial manufacture, use, sale, or offer for sale in the United States, or importation into the United States, of the Noratech ANDA Products prior to the expiration of the '918 patent, inclusive of any extensions and additional periods of exclusivity;

189. An order that the effective date of any approval of ANDA No. 213671 be a date that is not earlier than the expiration date of the '918 patent, inclusive of any extensions and additional periods of exclusivity;

190. Declaratory judgment that the commercial manufacture, use, sale, offer for sale, and/or importation of the Noratech ANDA Products will directly infringe one or more claims of the '918 patent;

191. Damages or other monetary relief from Defendant Noratech for the direct infringement of the '918 patent;

192. A declaration that this case is an exceptional case pursuant to 35 U.S.C. § 285 and an award of attorney's fees;

193. Novartis's costs and expenses in this action; and

194. Such other and further relief as the Court may deem just and proper.

Dated: October 24, 2022 OF COUNSEL: Nicholas N. Kallas Christina Schwarz Christopher E. Loh Susanne L. Flanders Jared L. Stringham Shannon K. Clark Laura K. Fishwick Gregory J. Manas VENABLE LLP 1290 Avenue of the Americas New York, New York 10104 (212) 218-2100 *nkallas@venable.com* *cschwarz@venable.com* *cloh@venable.com* *slflanders@venable.com* *jlstringham@venable.com* *skclark@venable.com* *lfishwick@venable.com* *gjmanas@venable.com*	MCCARTER & ENGLISH, LLP By: /s/ Daniel M. Silver Daniel M. Silver (#4758) Alexandra M. Joyce (#6423) Renaissance Centre 405 N. King Street, 8th Floor Wilmington, Delaware 19801 (302) 984-6300 *dsilver@mccarter.com* *ajoyce@mccarter.com* *Attorneys for Plaintiff Novartis Pharmaceuticals Corporation*

EXHIBIT A

US011096918B2

(12) **United States Patent**
Feng et al.

(10) **Patent No.: US 11,096,918 B2**
(45) **Date of Patent: *Aug. 24, 2021**

(54) **AMORPHOUS SOLID FORM OF COMPOUNDS CONTAINING S—N-VALERYL-N-{[2'-(1H-TETRAZOLE-5-YL)-BIPHENYL-4-YL]-METHYL}-VALINE AND (2R,4S)-5-BIPHENYL-4-YL-4-(3-CARBOXY-PROPIONYLAMINO)-2-METHYL-PENTANOIC ACID ETHYL ESTER MOIETIES AND SODIUM CATIONS**

(71) Applicant: **Novartis Pharmaceuticals Corporation**, East Hanover, NJ (US)

(72) Inventors: **Lili Feng**, Pine Brook, NJ (US); **Sven Erik Godtfredsen**, Chatham, NJ (US); **Paul Allen Sutton**, Getsville, NY (US); **Mahavir Prashad**, Montville, NJ (US); **Michael J. Girgis**, Montville, NJ (US); **Bin Hu**, Green Brook, NJ (US); **Yugang Liu**, Bridgewater, NJ (US); **Thomas J. Blacklock**, East Hanover, NJ (US); **Piotr Henryk Karpinski**, Lincoln Park, NJ (US)

(73) Assignee: **NOVARTIS PHARMACEUTICALS CORPORATION**, East Hanover, NJ (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **16/579,581**

(22) Filed: **Sep. 23, 2019**

(65) **Prior Publication Data**

US 2020/0016109 A1 Jan. 16, 2020

Related U.S. Application Data

(60) Continuation of application No. 16/006,252, filed on Jun. 12, 2018, now abandoned, which is a continuation of application No. 15/187,872, filed on Jun. 21, 2016, now abandoned, which is a division of application No. 14/311,788, filed on Jun. 23, 2014, now Pat. No. 9,388,134, which is a division of application No. 11/722,360, filed as application No. PCT/US2006/043710 on Nov. 8, 2006, now Pat. No. 8,877,938.

(60) Provisional application No. 60/822,086, filed on Aug. 11, 2006, provisional application No. 60/789,332, filed on Apr. 4, 2006, provisional application No. 60/735,541, filed on Nov. 10, 2005, provisional application No. 60/735,093, filed on Nov. 9, 2005.

(51) **Int. Cl.**

A61K 31/216	(2006.01)
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C07C 233/47	(2006.01)
C07D 257/04	(2006.01)
A61K 45/06	(2006.01)
A61K 31/4422	(2006.01)
A61K 31/5415	(2006.01)
C07D 207/50	(2006.01)

(52) **U.S. Cl.**

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(58) **Field of Classification Search**

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See application file for complete search history.

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(57) **ABSTRACT**

An amorphous solid form of a compound comprising the angiotensin receptor antagonist (ARB) valsartan, the neutral endopeptidase inhibitor (NEPi) (2R,4S)-5-biphenyl-4-yl-4-(3-carboxy-propionylamino)-2-methylpentanoic acid ethyl ester and sodium cations is provided. This compound is useful for the treatment of hypertension and/or heart failure.

2 Claims, 1 Drawing Sheet

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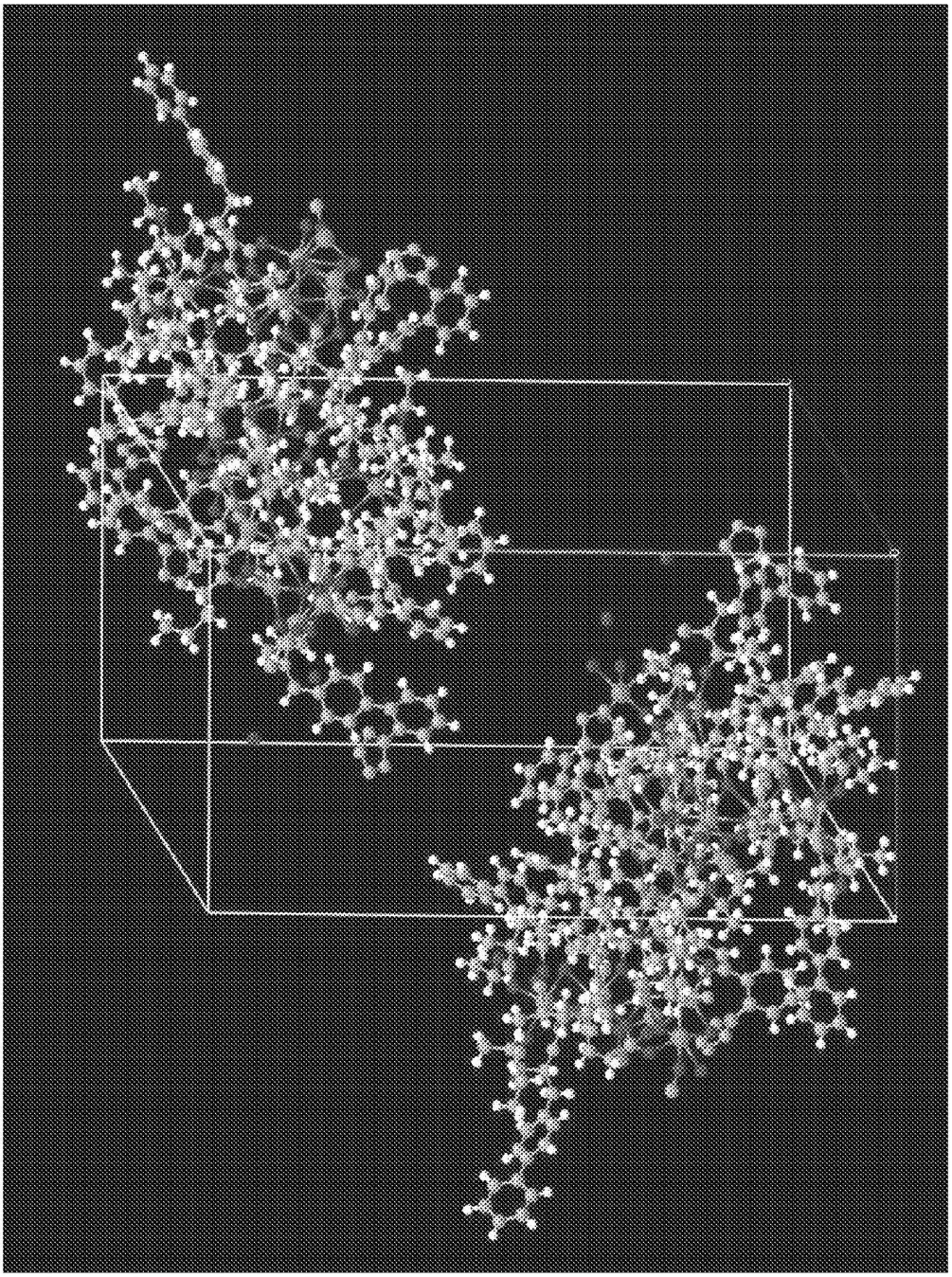


AMORPHOUS SOLID FORM OF COMPOUNDS CONTAINING S—N-VALERYL-N-{[2'-(1H-TETRAZOLE-5-YL)-BIPHENYL-4-YL]-METHYL}-VALINE AND (2R,4S)-5-BIPHENYL-4-YL-4-(3-CARBOXY-PROPIONYLAMINO)-2-METHYL-PENTANOIC ACID ETHYL ESTER MOIETIES AND SODIUM CATIONS

RELATED APPLICATIONS

This application is a continuation application of U.S. application Ser. No. 16/006,252, filed on Jun. 12, 2018, which is a continuation application of U.S. application Ser. No. 15/187,872, filed on Jun. 21, 2016, which is a divisional application of U.S. application Ser. No. 14/311,788, filed on Jun. 23, 2014, now U.S. Pat. No. 9,388,134, which is a divisional application of U.S. application Ser. No. 11/722,360, filed on Jan. 15, 2008, now U.S. Pat. No. 8,877,938, which is a national stage application, filed under 35 U.S.C. § 371, of International Application No. PCT/US06/43710, filed on Nov. 8, 2006, which claims the benefit of and priority to U.S. Provisional Application Nos. 60/822,086, filed Aug. 11, 2006, 60/789,332, filed Apr. 4, 2006, 60/735,541, filed on Nov. 10, 2005, and 60/735,093, filed on Nov. 9, 2005, the entire contents of each of which are incorporated herein by reference in their entireties.

FIELD OF THE INVENTION

The present invention is directed to dual-acting compounds and combinations of angiotensin receptor blockers and neutral endopeptidase inhibitors, in particular a dual acting molecule wherein the angiotensin receptor blocker and neutral endopeptidase inhibitor are linked via non-covalent bonding, or supramolecular complexes of angiotensin receptor blockers and neutral endopeptidase inhibitors, also described as linked pro-drugs, such as mixed salts or co-crystals, as well as to pharmaceutical combinations containing such a dual-acting compound or combination, methods of preparing such dual-acting compounds and methods of treating a subject with such a dual-acting compound or combination. Specifically, the invention is directed to a dual acting compound or supramolecular complex of two active agents having the same or different modes of action in one molecule.

BACKGROUND OF THE INVENTION

Angiotensin II is a hormone that causes blood vessels to constrict. This, in turn, can result in high blood pressure and strain on the heart. It is known that angiotensin II interacts with specific receptors on the surface of target cells. Two receptor subtypes for angiotensin II, namely AT1 and AT2, have been identified thus far. In recent times, great efforts have been made to identify substances that bind to the AT1 receptor. Angiotensin receptor blockers (ARBs, angiotensin II antagonists) are now known to prevent angiotensin II from binding to its receptors in the walls of blood vessels, thereby resulting in lower blood pressure. Because of the inhibition of the AT1 receptor, such antagonists can be used, therefore, as anti-hypertensives or for the treatment of congestive heart failure, among other indications.

Neutral endopeptidase (EC 3.4.24.11; enkephalinase; atriopeptidase; NEP) is a zinc-containing metalloprotease that cleaves a variety of peptide substrates on the amino side of hydrophobic residues [see Pharmacol Rev, Vol. 45, p. 87 (1993)]. Substrates for this enzyme include, but are not limited to, atrial natriuretic peptide (ANP, also known as ANF), brain natriuretic peptide (BNP), met- and leu-enkephalin, bradykinin, neurokinin A, endothelin-1 and substance P. ANP is a potent vasorelaxant and natriuretic agent [see J Hypertens, Vol. 19, p. 1923 (2001)]. Infusion of ANP in normal subjects resulted in a reproducible, marked enhancement of natriuresis and diuresis, including increases in fractional excretion of sodium, urinary flow rate and glomerular filtration rate [see J Clin Pharmacol, Vol. 27, p. 927 (1987)]. However, ANP has a short half-life in circulation, and NEP in kidney cortex membranes has been shown to be the major enzyme responsible for degrading this peptide [see Peptides, Vol. 9, p. 173 (1988)]. Thus, inhibitors of NEP (neutral endopeptidase inhibitors, NEPi) should increase plasma levels of ANP and, hence, are expected to induce natriuretic and diuretic effects.

While substances, such as angiotensin receptor blockers and neutral endopeptidase inhibitors may be useful in the control of hypertension, essential hypertension is a polygenic disease and is not always controlled adequately by monotherapy. Approximately 333 million adults in economically developed countries and about 65 million Americans (1 in 3 adults) had high blood pressure in 2000 [see Lancet, Vol. 365, p. 217 (2005); and Hypertension, Vol. 44, p. 398 (2004)]. Prolonged and uncontrolled hypertensive vascular disease ultimately leads to a variety of pathological changes in target organs, such as the heart and kidney.

Sustained hypertension can lead as well to an increased occurrence of stroke. Therefore, there is a strong need to evaluate the efficacy of anti-hypertensive therapy, an examination of additional cardiovascular endpoints, beyond those of blood pressure lowering, to get further insight into the benefits of combined treatment.

The nature of hypertensive vascular diseases is multifactorial. Under certain circumstances, drugs with different mechanisms of action have been combined. However, just considering any combination of drugs having different modes of action does not necessarily lead to combinations with advantageous effects. Accordingly, there is a need for efficacious combination therapy which does not have deleterious side effects.

SUMMARY OF THE INVENTION

In a first aspect, the present invention is directed to a dual-acting compound, such as a supramolecular complex, comprising:

(a) an angiotensin receptor antagonist;

(b) a neutral endopeptidase inhibitor (NEPi); and optionally

(c) a pharmaceutically acceptable cation.

The present invention is also directed to a dual-acting compound, such as a supramolecular complex, obtainable by:

(i) dissolving an angiotensin receptor antagonist and a neutral endopeptidase inhibitor (NEPi) in a suitable solvent;

(ii) dissolving a basic compound of Cat in a suitable solvent, wherein Cat is a cation;

(iii) combining the solutions obtained in steps (i) and (ii);

(iv) precipitation of the solid, and drying same to obtain the dual-acting compound; or alternatively obtaining the dual-acting compound by exchanging the solvent(s) employed in steps (i) and (ii) by

(iva) evaporating the resulting solution to dryness;

(va) re-dissolving the solid in a suitable solvent;

(via) precipitation of the solid and drying same to obtain the dual-acting compound.

The present invention is also directed to linked pro-drugs comprising:

(a) an angiotensin receptor antagonist or a pharmaceutically acceptable salt thereof; and

(b) a NEPi or a pharmaceutically acceptable salt thereof, wherein the angiotensin receptor antagonist or a pharmaceutically acceptable salt thereof and the NEPi or a pharmaceutically acceptable salt thereof are linked by a linking moiety.

The present invention is also directed to a combination comprising:

(a) a pharmaceutically acceptable salt of an angiotensin receptor antagonist; and

(b) a pharmaceutically acceptable salt of a neutral endopeptidase inhibitor (NEPi);

wherein the pharmaceutically acceptable salt of the angiotensin receptor antagonist and the NEPi is the same and is selected from a salt of Na, K or NH_4.

In preferred embodiments, the angiotensin receptor antagonist and NEPi have acidic groups which facilitate formation of the dual acting compound, such as the supramolecular complex of the present invention.

Preferably, the angiotensin receptor antagonist is selected from the group consisting of valsartan, losartan, irbesartan, telmisartan, eprosartan, candesartan, olmesartan, saprisartan, tasosartan, elisartan and combinations thereof.

In preferred embodiments, the NEPi is selected from the group consisting of: SQ 28,603; N—[N-[1(S)-carboxyl-3-phenylpropyl]-(S)-phenylalanyl]-(S)-isoserine; N—[N-[((1S)-carboxy-2-phenyl)ethyl]-(S)-phenylalanyl]-β-alanine; N-[2(S)-mercaptomethyl-3-(2-methylphenyl)-propionyl]methionine; (cis-4-[[[1-[2-carboxy-3-(2-methoxyethoxy)propyl]-cyclopentyl]carbonyl]amino]-cyclohexanecarboxylic acid); thiorphan; retro-thiorphan; phosphoramidon; SQ 29072; N-(3-carboxy-1-oxopropyl)-(4S)-p-phenylphenylmethyl)-4-amino-2R-methylbutanoic acid ethyl ester; (S)-cis-4-[1-[2-(5-indanyloxycarbonyl)-3-(2-methoxyethoxy)propyl]-1-cyclopentanecarboxamido]-1-cyclohexanecarboxylic acid; 3-(1-[6-endo-hydroxymethyl-bicyclo[2,2,1]heptane-2-exo-carbamoyl]cyclopentyl)-2-(2-methoxyethyl)propanoic acid; N-(1-(3-(N-t-butoxycarbonyl-(S)-prolylamino)-2(S)-t-butoxy-carbonylpropyl)cyclopentanecarbonyl)-O-benzyl-(S)-serine methyl ester; 4-[[2-(mercaptomethyl)-1-oxo-3-phenylpropyl]amino]benzoic acid; 3-[1-(cis-4-carboxycarbonyl-cis-3-butylcyclohexyl-r-1-carbamoyl)cyclopentyl]-2S-(2-methoxyethoxymethyl)propanoic acid; N-((2S)-2-(4-biphenylmethyl)-4-carboxy-5-phenoxyvaleryl)glycine; N-(1-(N-hydroxycarbamoylmethyl)-1-cyclopentanecarbonyl)-L-phenylalanine; (S)-(2-biphenyl-4-yl)-1-(1H-tetrazol-5-yl)ethylamino) methylphosphonic acid; (S)-5-(N-(2-(phosphonomethylamino)-3-(4-biphenyl)propionyl)-2-aminoethyl)tetrazole; β-alanine; 3-[1,1'-biphenyl]-4-yl-N-[diphenoxyphosphinyl)methyl]-L-alanyl; N-(2-carboxy-4-thienyl)-3-mercapto-2-benzylpropanamide; 2-(2-mercaptomethyl-3-phenylpropionamido)thiazol-4-ylcarboxylic acid; (L)-(1-((2,2-dimethyl-1,3-dioxolan-4-yl)-methoxy)carbonyl)-2-phenylethyl)-L-phenylalanyl)-β-alanine; N—[N-[(L)-[1-[(2,2-dimethyl-1,3-dioxolan-4-yl)-methoxy]carbonyl]-2-phenylethyl]-L-phenylalanyl]-(R)-alanine; N—[N-[(L)-1-carboxy-2-phenylethyl]-L-phenylalanyl]-(R)-alanine; N-[2-acetylthiomethyl-3-(2-methyl-phenyl)propionyl]-methionine ethyl ester; N-[2-mercaptomethyl-3-(2-methylphenyl)propionyl]-methionine; N-[2(S)-mercaptomethyl-3-(2-methylphenyl)propanoyl]-(S)-isoserine; N—(S)-[3-mercapto-2-(2-methylphenyl)propionyl]-(S)-2-methoxy-(R)-alanine; N-[1-[[1(S)-benzyloxy-carbonyl-3-phenylpropyl]amino]cyclopentylcarbonyl]-(S)-isoserine; N-[1-[[1(S)-carbonyl-3-phenylpropyl]amino]-cyclopentylcarbonyl]-(S)-isoserine; 1,1'-[dithiobis-[2(S)-(2-methylbenzyl)-1-oxo-3,1-propanediyl]]-bis-(S)-isoserine; 1,1'-[dithiobis-[2(S)-(2-methylbenzyl)-1-oxo-3,1-propanediyl]]-bis-(S)-methionine; N-(3-phenyl-2-(mercaptomethyl)-propionyl)-(S)-4-(methylmercapto)methionine; N-[2-acetylthiomethyl-3-phenyl-propionyl]-3-aminobenzoic acid; N-[2-mercaptomethyl-3-phenyl-propionyl]-3-aminobenzoic acid; N-[1-(2-carboxy-4-phenylbutyl)-cyclopentane-carbonyl]-(S)-isoserine; N-[1-(acetylthiomethyl)cyclopentane-carbonyl]-(S)-methionine ethyl ester; 3(S)-[2-(acetylthiomethyl)-3-phenyl-propionyl]amimo-ε-caprolactam; N-(2-acetylthiomethyl-3-(2-methylphenyl) propionyl)-methionine ethyl ester; and combinations thereof. Preferably, the dual-acting compound or combination, in particular the supramolecular complex, is a mixed salt or a co-crystal. It is also preferred that the linked pro-drug is a mixed salt or a co-crystal.

In a second aspect, the present invention is directed to pharmaceutical composition comprising

(a) the aforementioned dual-acting compound or combination, such as the aforementioned complex; and

(b) at least one pharmaceutically acceptable additive.

The present invention is also directed to pharmaceutical compositions comprising a linked pro-drug comprising:

(a) an angiotensin receptor antagonist or a pharmaceutically acceptable salt thereof;

(b) a NEPi or a pharmaceutically acceptable salt thereof, wherein the angiotensin receptor antagonist or a pharmaceutically acceptable salt thereof and the NEPi or a pharmaceutically acceptable salt thereof are linked by a linking moiety; and

(c) at least one pharmaceutically acceptable additive.

In a third aspect, the present invention is directed to a method of preparing a dual-acting compound, in particular a supramolecular complex, comprising

(a) an angiotensin receptor antagonist;

(b) a neutral endopeptidase inhibitor (NEPi); and optionally

(c) a pharmaceutically acceptable cation selected from the group consisting of Na, K and NH_4;

said method comprising the steps of:

(i) dissolving an angiotensin receptor antagonist and a neutral endopeptidase inhibitor (NEPi) in a suitable solvent;

(ii) dissolving a basic compound of Cat in a suitable solvent, wherein Cat is a cation;

(iii) combining the solutions obtained in steps (i) and (ii);

(iv) precipitation of the solid, and drying same to obtain the dual-acting compound; or alternatively obtaining the dual-acting compound by exchanging the solvent(s) employed in steps (i) and (ii) by

(iva) evaporating the resulting solution to dryness;

(va) re-dissolving the solid in a suitable solvent;

(via) precipitation of the solid and drying same to obtain the dual-acting compound.

The present invention is also directed to a method of making a linked pro-drug comprising:

(a) an angiotensin receptor antagonist or a pharmaceutically acceptable salt thereof;

(b) a NEPi or a pharmaceutically acceptable salt thereof, wherein the angiotensin receptor antagonist or a pharmaceutically acceptable salt thereof and the NEPi or a pharmaceutically acceptable salt thereof are linked by

a linking moiety; and comprising adding a linking moiety and a solvent to a mixture of an angiotensin receptor antagonist and a NEPi; and

(d) isolating the linked pro-drug.

In a fourth aspect, this invention is directed to a method of treating or preventing a disease or condition, such as hypertension, heart failure (acute and chronic), congestive heart failure, left ventricular dysfunction and hypertrophic cardiomyopathy, diabetic cardiac myopathy, supraventricular and ventricular arrhythmias, atrial fibrillation, atrial flutter, detrimental vascular remodeling, myocardial infarction and its sequelae, atherosclerosis, angina (unstable or stable), renal insufficiency (diabetic and non-diabetic), heart failure, angina pectoris, diabetes, secondary aldosteronism, primary and secondary pulmonary hypertension, renal failure conditions, such as diabetic nephropathy, glomerulonephritis, scleroderma, glomerular sclerosis, proteinuria of primary renal disease, and also renal vascular hypertension, diabetic retinopathy, other vascular disorders, such as migraine, peripheral vascular disease, Raynaud's disease, luminal hyperplasia, cognitive dysfunction (such as Alzheimer's), glaucoma and stroke comprising administering the afore-mentioned dual-acting compound or combination, in particular the supramolecular complex, or the afore-mentioned linked pro-drug, preferably, the complex, to a subject in need of such treatment.

BRIEF DESCRIPTION OF THE DRAWING

FIG. 1 shows a pictorial representation of the unit cell of the supramolecular complex of trisodium [3-((1 S,3R) −1-biphenyl-4-y lmethyl-3-ethoxy carbonyl-1-butylcarbamoyl)propionate-(S)-3 '-methyl-2'-(pentanoyl {2 "-(tetrazol-5-ylate)biphenyl-4'-y 'methyl} amino)butyrate] hemipentahydrate comprising two asymmetric units. The following color code is used: grey=carbon atom; blue=nitrogen atom; red=oxygen atom; violet=sodium atom.

DETAILED DESCRIPTION

The present invention relates to a dual-acting compound or combination, in particular a supramolecular complex, or linked pro-drug or in particular a supramolecular complex of two active agents with different mechanisms of action, namely an angiotensin receptor antagonist and a neutral endopeptidase inhibitor, which can form a unique molecular entity for the treatment of patients with various cardiovascular and/or renal diseases.

One embodiment of the invention is directed to a physical combination comprising:

(a) a pharmaceutically acceptable salt of an angiotensin receptor antagonist; and

(b) a pharmaceutically acceptable salt of a neutral endopeptidase inhibitor (NEPi); wherein the pharmaceutically acceptable salt of the angiotensin receptor antagonist and the NEPi is the same and is selected from a salt of Na, K or NH_4.

Specifically, it is preferred that the two active agents are combined with each other so as to form a single dual-acting compound, in particular a supramolecular complex. By doing so, a new molecular or supramolecular entity is formed having distinct properties different to the above physical combination.

Thus, the present invention is directed to a dual-acting compound, in particular a supramolecular complex, comprising:

(a) an angiotensin receptor antagonist;

(b) a neutral endopeptidase inhibitor (NEPi); and

(c) a pharmaceutically acceptable cation preferably selected from the group consisting of Na, K and NH_4.

The present invention is also directed to a dual-acting compound, in particular a supramolecular complex, obtainable by:

(i) dissolving an angiotensin receptor antagonist and a neutral endopeptidase inhibitor (NEPi) in a suitable solvent;

(ii) dissolving a basic compound of Cat such as (Cat)OH, $(Cat)_2CO_3$, $(Cat)HCO_3$ in a suitable solvent, wherein Cat is a cation preferably selected from the group consisting of Na, K and NH_4;

(iii) combining the solutions obtained in steps (i) and (ii);

(iv) precipitation of the solid, and drying same to obtain the dual-acting compound; or alternatively obtaining the dual-acting compound by exchanging the solvent(s) employed in steps (i) and (ii) by

(iva) evaporating the resulting solution to dryness;

(va) re-dissolving the solid in a suitable solvent;

(via) precipitation of the solid and drying same to obtain the dual-acting compound.

The present invention is further directed to linked pro-drugs comprising:

(a) an angiotensin receptor antagonist or a pharmaceutically acceptable salt thereof; and

(b) a NEPi or a pharmaceutically acceptable salt thereof, wherein the angiotensin receptor antagonist or a pharmaceutically acceptable salt thereof and the NEPi or a pharmaceutically acceptable salt thereof are linked by a linking moiety.

The two components are each linked to a linking moiety thereby creating a linked pro-drug.

Preferably, the linked pro-drug is substantially pure; as used herein, "substantially pure" refers to at least 90%, more preferably at least 95% and most preferably at least 98% purity.

As one preferred embodiment of the present invention, the linked pro-drug has a structure such that by linking the two components with the linking moiety, a supramolecular complex is formed.

For the purpose of the present invention, the term "dual-acting compound" is intended to describe that these compounds have two different modes of action in one compound, one is the angiotensin receptor blockade resulting from the ARB molecular moiety of the compound and the other is the neutral endopeptidase inhibition resulting from the NEPi molecular moiety of the compound.

For the purpose of the present invention, the term "compound" is intended to describe a chemical substance comprising covalent bonds within the two pharmaceutically active agents, the ARB and the NEPi molecular moieties, and non-covalent interactions between these two pharmaceutically active agents, the ARB and the NEPi molecular moieties.

Typically, hydrogen bonding can be observed between the two pharmaceutically active agents, the ARB and the NEPi molecular moieties. Ionic bonds can be present between the cation and one or both of the two pharmaceutically active agents, the ARB and the NEPi molecular moieties. Other types of bonds may also be present within the compound

such as van der Waals forces. For illustrative purposes, the dual-acting compound of the present invention could be represented as follows:

$$(ARB)\text{-}(L)_m\text{-}(NEPi)$$

wherein L is a linking moiety, such as a cation or is a noncovalent bond and m is an integer from 1 or more. In other words the ARB and NEPi moiety can be connected via non-covalent bonds such as hydrogen bonding. Alternatively or additionally they may be connected via a linking moiety such as a cation.

In one embodiment, the dual-acting compound may be considered to be a linked pro-drug, whereby the linking moiety, such as the cation, linking the two pharmaceutically active agents, the ARB and the NEPi, forms the pro-drug of these agents which are released once the linked pro-drug is ingested and absorbed.

In a preferred embodiment, the dual-acting compound is a complex, in particular a supramolecular complex.

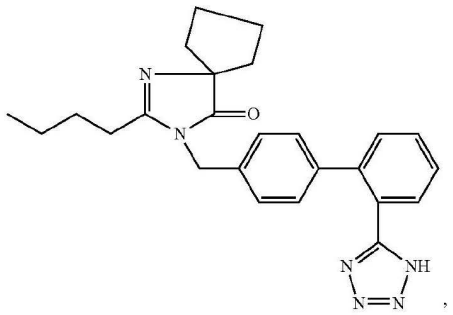
For the purpose of the present invention, the term "supramolecular complex" is intended to describe an interaction between the two pharmaceutically active agents, the cations and any other entity present such as a solvent, in particular water, by means of noncovalent, intermolecular bonding between them. This interaction leads to an association of the species present in the supramolecular complex distinguishing this complex over a physical mixture of the species.

The noncovalent intermolecular bonding can be any interactions known in the art to form such supramolecular complexes, such as hydrogen bonding, van der Waals forces and π-π stacking. Ionic bonds can also be present. Preferably, there exists ionic bonding and additionally hydrogen bonding to form a network of interactions within the complex. The supramolecular complex exists preferably in the solid state but may also be present in liquid media. As a preferred embodiment of the invention, the complex is crystalline and in this case is preferably a mixed crystal or co-crystal.

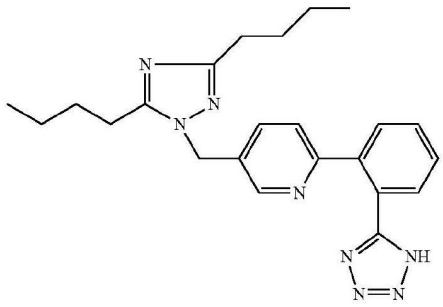
Typically, the dual-acting compound, in particular the supramolecular complex shows properties such as melting point, IR spectrum etc. that are different from a physical mixture of the species.

Preferably, the dual-acting compound, in particular the supramolecular complex, has a network of non-covalent bonds, in particular hydrogen bonds, between the two pharmaceutically active agents and any solvent, if present, preferably water. Moreover, it is preferred that the dual-acting compound, in particular the supramolecular complex, has a network of non-covalent bonds, in particular ionic and hydrogen bonds, between the two pharmaceutically active agents, the cation and any solvent, if present, preferably water. The cation is preferably coordinated to several oxygen ligands, thus, providing a linkage between these oxygen ligands. The oxygen ligands come from the carbonyl and carboxylate groups present in the two pharmaceutically active agents and preferably also from any solvent, if present, preferably water.

The dual acting compound comprises a molecular moiety of an angiotensin receptor antagonist. This means that a molecular moiety derived from an angiotensin receptor antagonist is participating in the build-up of the dual-acting compound. The angiotensin receptor antagonist is part of the compound and connected to the NEP inhibitor directly or indirectly via non-covalent bonds. For sake of convenience, throughout the application, the term "angiotensin receptor antagonist" will be used when describing this part of the compound. Angiotensin receptor antagonists (ARBs) suitable for use in the present invention include, without limitation, valsartan, losartan, irbesartan, telmisartan, eprosartan, candesartan, olmesartan saprisartan, tasosartan, elisartan, the compound with the designation E-1477 of the following formula

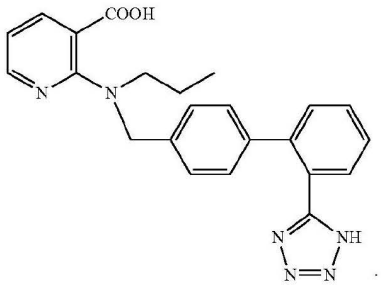


the compound with the designation SC-52458 of the following formula



and

the compound with the designation the compound ZD-8731 of the following formula



Suitable angiotensin II receptor antagonist also includes, but is not limited to, saralasin acetate, candesartan cilexetil, CGP-63170, EMD-66397, KT3-671, LR-B/081, valsartan, A-81282, BIBR-363, BIBS-222, BMS-184698, candesartan, CV-11194, EXP-3174, KW-3433, L-161177, L-162154, LR-B/057, LY-235656, PD-150304, U-96849, U-97018, UP-275-22, WAY-126227, WK-1492.2K, YM-31472, losartan potassium, E-4177, EMD-73495, eprosartan, HN-65021, irbesartan, L-159282, ME-3221, SL-91.0102, Tasosartan, Telmisartan, UP-269-6, YM-358, CGP-49870, GA-0056,

L-159689, L-162234, L-162441, L-163007, PD-123177, A-81988, BMS-180560, CGP-38560A, CGP-48369, DA-2079, DE-3489, DuP-167, EXP-063, EXP-6155, EXP-6803, EXP-7711, EXP-9270, FK-739, HR-720, ICI-D6888, ICI-D7155, ICI-D8731, isoteoline, KRI-1177, L-158809, L-158978, L-159874, LR B087, LY-285434, LY-302289, LY-315995, RG-13647, RWJ-38970, RWJ-46458, S-8307, S-8308, saprisartan, saralasin, Sarmesin, WK-1360, X-6803, ZD-6888, ZD-7155, ZD-8731, BIBS39, CI-996, DMP-811, DuP-532, EXP-929, L-163017, LY-301875, XH-148, XR-510, zolasartan and PD-123319.

Also included within the scope of this aspect of the invention are combinations of the above-identified ARBs.

ARBs to be used for preparing the combination or complex in accordance with the present invention can be purchased from commercial sources or can be prepared according to known methods. ARBs may be used for purposes of this invention in their free form, as well as in any suitable salt or ester form.

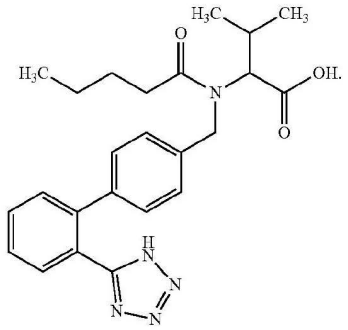
Preferred salts forms include acid addition salts. The compounds having at least one acid group (e.g., COOH or 5-tetrazolyl) can also form salts with bases. Suitable salts with bases are, e.g., metal salts, such as alkali metal or alkaline earth metal salts, e.g., sodium, potassium, calcium or magnesium salts, or salts with ammonia or an organic amine, such as morpholine, thiomorpholine, piperidine, pyrrolidine, a mono-, di- or tri-lower alkylamine, e.g., ethyl-, tert-butyl-, diethyl-, diisopropyl-, triethyl-, tributyl- or dimethylpropylamine, or a mono-, di- or trihydroxy lower alkylamine, e.g., mono-, di- or tri-ethanolamine. Corresponding internal salts may furthermore be formed. Salts which are unsuitable for pharmaceutical uses but which can be employed, e.g., for the isolation or purification of free compounds I or their pharmaceutically acceptable salts, are also included. Even more preferred salts are, e.g., selected from the mono-sodium salt in amorphous form; di-sodium salt of valsartan in amorphous or crystalline form, especially in hydrate form, thereof.

Mono-potassium salt of valsartan in amorphous form; di-potassium salt of valsartan in amorphous or crystalline form, especially in hydrate form, thereof.

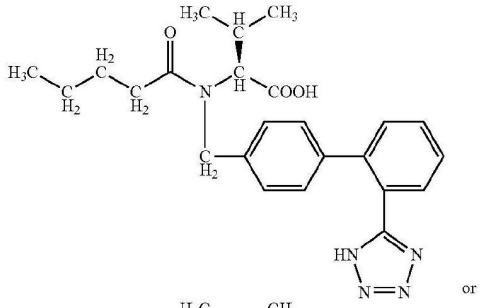
Calcium salt of valsartan in crystalline form, especially in hydrate form, primarily the tetrahydrate thereof; magnesium salt of valsartan in crystalline form, especially in hydrate form, primarily the hexahydrate thereof; calcium/magnesium mixed salt of valsartan in crystalline form, especially in hydrate form; bis-diethylammonium salt of valsartan in crystalline form, especially in hydrate form; bis-dipropylammonium salt of valsartan in crystalline form, especially in hydrate form; bis-dibutylammonium salt of valsartan in crystalline form, especially in hydrate form, primarily the hemihydrate thereof; mono-L-arginine salt of valsartan in amorphous form; bis-L-arginine salt of valsartan in amorphous form; mono-L-lysine salt of valsartan in amorphous form; bis-L-lysine salt of valsartan in amorphous form.

Preferably when preparing the dual-acting compound, in particular the complex according to the present invention, the free form of the ARB is used.

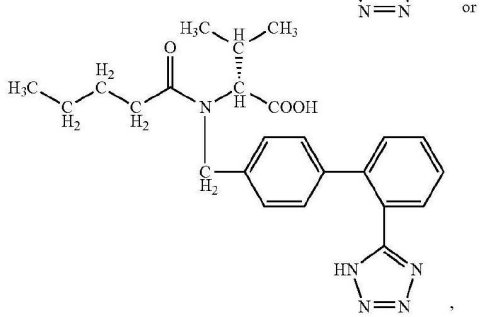
In a preferred embodiment of this invention, the angiotensin receptor blocker used in the combination or complex of the present invention is Valsartan the molecular structure of which is shown below



Valsartan may be in the racemic form or as one of the two isomers shown below

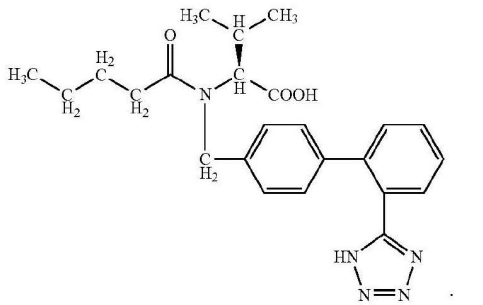


or



,

preferably



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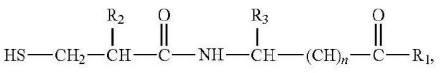
Valsartan ((S)—N-valeryl-N-{[2'-(1H-tetrazole-5-yl)-biphenyl-4-yl]-methyl}-valine) used according to the present invention can be purchased from commercial sources or can be prepared according to known methods. For example, the preparation of valsartan is described in U.S. Pat. No. 5,399,578 and EP 0 443 983, the entire disclosure of each of which is incorporated by reference herein. Valsartan may be used for purposes of this invention in its free acid form, as well as in any suitable salt form. Additionally, esters or other derivatives of the carboxylic grouping may be applied for the synthesis of linked pro-drugs, as well as salts and derivatives of the tetrazole grouping. Reference to ARBs includes reference to pharmaceutically acceptable salts thereof.

Preferably, the ARB is a diprotic acid. Thus, the angiotensin receptor blocker has a charge of 0, 1 or 2 depending on the pH of the solution.

In the combination of the present invention, the ARB is in the form of a pharmaceutically acceptable salt selected from Na, K or NH_4, preferably Na. This includes both the mono- and di-salt of these cations, preferably the di-salt. In particular in the case of valsartan this means that both the carboxylic acid moiety and the tetrazole moiety form the salt.

In the dual-acting compound, in particular the supramolecular complex of the present invention, typically the free form of the ARB is employed in the preparation and the cationic species present in the complex is introduced by using a base, e.g. (Cat)OH.

The dual acting compound comprises a molecular moiety of a neutral endopeptidase inhibitor. This means that a molecular moiety derived from a neutral endopeptidase inhibitor is participating in the build-up of the dual-acting compound. The neutral endopeptidase inhibitor is part of the compound and connected to the ARB directly or indirectly via non-covalent bonds. For sake of convenience, throughout the application, the term "neutral endopeptidase inhibitor" will be used when describing this part of the compound. Neutral endopeptidase inhibitors suitable for use in the present invention include those of formula (I)



(I)

wherein

R_2 is alkyl of 1-7 carbons, trifluoromethyl, phenyl, substituted phenyl, —(CH_2)1 to 4-phenyl, or —(CH_2)1 to 4-substituted phenyl;

R_3 is hydrogen, alkyl of 1-7 carbons, phenyl, substituted phenyl, —(CH_2)1 to 4-phenyl or —(CH_2)1 to 4-substituted phenyl;

R_1 is hydroxy, alkoxy of 1-7 carbons or NH_2;

n is an integer from 1-15;

and the term substituted phenyl refers to a substituent selected from lower alkyl of 1-4 carbons, lower alkoxy of 1-4 carbons, lower alkylthio of 1-4 carbons, hydroxy, CI, Br or F.

Preferred neutral endopeptidase inhibitors of formula (I) include compounds,

wherein

R_2 is benzyl;

R_3 is hydrogen;

n is an integer from 1-9; and

R_1 is hydroxy.

Another preferred neutral endopeptidase inhibitor is (3S,2'R)-3-{1-[2'-(ethoxycarbonyl)-4'-phenyl-butyl]-cyclopentan-1-carbonylamino}-2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepine-1-acetic acid or a pharmaceutically acceptable salt thereof.

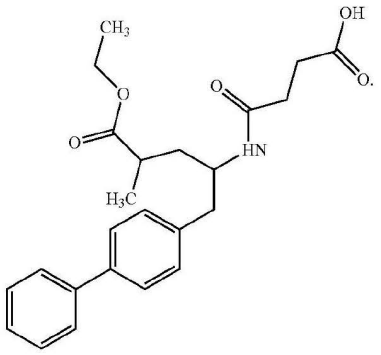
Preferred neutral endopeptidase inhibitors suitable for use in the present invention include, without limitation, SQ 28,603; N—[N-[1(S)-carboxyl-3-phenylpropyl]-(S)-phenylalanyl]-(S)-isoserine; N—[N-[((1S)-carboxy-2-phenyl)ethyl]-(S)-phenylalanyl]-β-alanine; N-[2(S)-mercaptomethyl-3-(2-methylphenyl)-propionyl]methionine; (cis-4-[[[1-[2-carboxy-3-(2-methoxyethoxy)propyl]-cyclopentyl]carbonyl]amino]-cyclohexanecarboxylic acid); thiorphan; retro-thiorphan; phosphoramidon; SQ 29072; (2R,4S)-5-biphenyl-4-yl-4-(3-carboxy-propionylamino)-2-methylpentanoic acid ethyl ester; N-(3-carboxy-1-oxopropyl)-(4S)-p-phenylphenylmethyl)-4-amino-2R-methylbutanoic acid; (S)-cis-4-[1-[2-(5-indanyloxycarbonyl)-3-(2-methoxyethoxy)propyl]-1-cyclopentanecarboxamido]-1-cyclohexanecarboxylic acid; 3-(1-[6-endo-hydroxymethylbicyclo[2,2,1]heptane-2-exo-carbamoyl]cyclopentyl)-2-(2-methoxyethyl)propanoic acid; N-(1-(3-(N-t-butoxycarbonyl-(S)-prolylamino)-2(S)-t-butoxycarbonylpropyl)cyclopentanecarbonyl)-O-benzyl-(S)-serine methyl ester; 4-[[2-(mercaptomethyl)-1-oxo-3-phenylpropyl]amino]benzoic acid; 3-[1-(cis-4-carboxycarbonyl-cis-3-butylcyclohexyl-r-1-carbamoyl)cyclopentyl]-2S-(2-methoxyethoxymethyl)propanoic acid; N-((2S)-2-(4-biphenylmethyl)-4-carboxy-5-phenoxyvaleryl)glycine; N-(1-(N-hydroxycarbamoylmethyl)-1-cyclopentanecarbonyl)-L-phenylalanine; (S)-(2-biphenyl-4-yl)-1-(1H-tetrazol-5-yl)ethylamino) methylphosphonic acid; (S)-5-(N-(2-(phosphonomethylamino)-3-(4-biphenyl)propionyl)-2-aminoethyl)tetrazole; β-alanine; 3-[1,1'-biphenyl]-4-yl-N-[diphenoxyphosphinyl)methyl]-L-alanyl; N-(2-carboxy-4-thienyl)-3-mercapto-2-benzylpropanamide; 2-(2-mercaptomethyl-3-phenylpropionamido)thiazol-4-ylcarboxylic acid; (L)-(1-((2,2-dimethyl-1,3-dioxolan-4-yl)-methoxy)carbonyl)-2-phenylethyl)-L-phenylalanyl)-β-alanine; N—[N-[(L)-[1-[(2,2-dimethyl-1,3-dioxolan-4-yl)-methoxy]carbonyl]-2-phenylethyl]-L-phenylalanyl]-(R)-alanine; N—[N-[(L)-1-carboxy-2-phenylethyl]-L-phenylalanyl]-(R)-alanine; N-[2-acetylthiomethyl-3-(2-methyl-phenyl)propionyl]-methionine ethyl ester; N-[2-mercaptomethyl-3-(2-methylphenyl)propionyl]-methionine; N-[2(S)-mercaptomethyl-3-(2-methylphenyl)propanoyl]-(S)-isoserine; N—(S)-[3-mercapto-2-(2-methylphenyl)propionyl]-(S)-2-methoxy-(R)-alanine; N-[1-[[1(S)-benzyloxycarbonyl-3-phenylpropyl]amino]cyclopentylcarbonyl]-(S)-isoserine; N-[1-[[1(S)-carbonyl-3-phenylpropyl]amino]-cyclopentylcarbonyl]-(S)-isoserine; 1,1'-[dithiobis-[2(S)-(2-methylbenzyl)-1-oxo-3,1-propanediyl]]-bis-(S)-isoserine; 1,1'-[dithiobis-[2(S)-(2-methylbenzyl)-1-oxo-3,1-propanediyl]]-bis-(S)-methionine; N-(3-phenyl-2-(mercaptom-

ethyl)-propionyl)-(S)-4-(methylmercapto)methionine; N-[2-acetylthiomethyl-3-phenyl-propionyl]-3-aminobenzoic acid; N-[2-mercaptomethyl-3-phenyl-propionyl]-3-aminobenzoic acid; N-[1-(2-carboxy-4-phenylbutyl)-cyclopentane-carbonyl]-(S)-isoserine; N-[1-(acetylthiomethyl)cyclopentane-carbonyl]-(S)-methionine ethyl ester; 3(S)-[2-(acetylthiomethyl)-3-phenyl-propionyl]amimo-ε-caprolactam; N-(2-acetylthiomethyl-3-(2-methylphenyl) propionyl)-methionine ethyl ester; and combinations thereof.

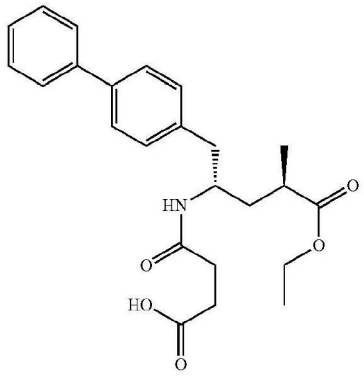
Neutral endopeptidase inhibitors can be purchased from commercial sources or can be prepared according to known methods, such as those set forth in any of U.S. Pat. Nos. 4,722,810, 5,223,516, 4,610,816, 4,929,641, South African Patent Application 84/0670, UK 69578, U.S. Pat. No. 5,217,996, EP 00342850, GB 02218983, WO 92/14706, EP 00343911, JP 06234754, EP 00361365, WO 90/09374, JP 07157459, WO 94/15908, U.S. Pat. Nos. 5,273,990, 5,294,632, 5,250,522, EP 00636621, WO 93/09101, EP 00590442, WO 93/10773, U.S. Pat. No. 5,217,996, the disclosure of each of which is incorporated by reference. Neutral endopeptidase inhibitors may be used for purposes of this invention in their free form, as well as in any suitable salt form. Reference to neutral endopeptidase inhibitors includes reference to pharmaceutically acceptable salts thereof.

Additionally esters or other derivatives of any carboxylic grouping may be applied for the synthesis of linked pro-drugs, as well as salts and derivatives of any other acidic grouping. In a preferred embodiment of this invention, the NEPi is 5-biphenyl-4-yl-4-(3-carboxy-priopionylamino)-2-methyl-pentanoic acid ethyl ester of formula (II) or the respective hydrolysed form 5-biphenyl-4-yl-4-(3-carboxy-priopionylamino)-2-methyl-pentanoic acid.

(II)



The compound of formula (II) can exist as the (2R,4S), (2R,4S), (2R,4S) or (2R,4S) isomer. Preferred is (2R,4S)-5-biphenyl-4-yl-4-(3-carboxy-propionylamino)-2-methyl-pentanoic acid ethyl ester as shown below:



The compound of formula (II) is a specific inhibitor of NEP and is described in U.S. Pat. No. 5,217,996. It can be purchased from commercial sources or can be prepared according to known methods. The compound of formula (II) may be used for purposes of this invention in its free form, as well as in any suitable salt or ester form.

Preferably the NEPi is a monoprotic acid. Thus, the NEPi has a charge of 0 or 1 depending on the pH of the solution.

In the combination of the present invention, the NEPi is in the form of a pharmaceutically acceptable salt selected from Na, K or NH_4, preferably Na.

In the dual-acting compound, in particular the supramolecular complex of the present invention, typically the free form of the NEPi is employed in the preparation and the cationic species present in the complex is introduced by using a base, (Cat)OH.

The dual acting compound preferably comprises non-covalent bonds between the ARB and the NEPi. Alternatively or in addition, it optionally comprises a linking moiety such as a pharmaceutically acceptable cation.

The linking moiety includes, but is not limited to, generally regarded as safe (GRAS) compounds or other pharmacologically acceptable compounds. The linking moiety may be an ion or a neutral molecule. In the case wherein the linking moiety is an ion the linked pro-drug is a salt and when the linking moiety is a neutral molecule the linked pro-drug is a co-crystal. Without being bound by any particular theory, the acidic portion of the ARB and NEPi donate a proton to the basic linking moiety such that all three components then become united to form one molecule. When the linked pro-drug is ingested by the subject intended to be treated the more acidic nature of the ingestion environment causes the linked pro-drug to separate into individual components concomitant with ingestion and absorption and therefore be converted into active agents to provide their beneficial biological action to treat the intended diseases.

In the case of a linked pro-drug salt or the dual-acting compound, the linking moiety or the cation, respectively, is preferably a positively charged mono-, di- or tri-valent cation, an organic base or an amino acid. Preferred cations (Cat) both for the linked pro-drug in general and the dual-acting compound, in particular the complex are basic cations, even more preferably metallic cations. Preferred metallic cations include, but are not limited to Na, K, Ca, Mg, Zn,

Fe or NH_4. Amine bases and salt forming agents may also be employed, such as benzathine, hydrabamine, ethylenediamine, n-n-dibenzyl-ethylenediamine, L-arginine, choline hydroxide, N-methyl-glucamine, (Meglumine), L-Lysine, dimethylaminoethanol (Deanol), t-butylamine, diethylamine, 2-(diethylamino)-ethanol, 4-(2-hydroxyethyl)-morpholine, Thromethanine (TRIS), 4-acetamidophenol, 2-amino-2-methyl-1,3-propanediol, 2-amino-2-methyl-propanol, benzylamine, cyclohexylamine, diethanolamine, ethanolamine, imidazole, piperazine and triethanolamine.

Most preferably, the cation is Na, K or NH_4, such as Na. In one embodiment Ca is preferred.

In the case of a linked pro-drug co-crystal, the linking moiety is may also be a neutral molecule which provides hydrogen-bonding functionality.

In one embodiment, the linked pro-drugs of this invention are represented as set forth below, wherein scheme (1) and (2) represent a salt and scheme (3) represents a co-crystal:

NEPi·Xa·ARB scheme (1)

NEPi·XaYb·ARB scheme (2)

NEPi·Zc·ARB scheme (3),

wherein

X is Ca, Mg, Zn or Fe;

Y is Na, K or NH4;

Z is a neutral molecule; and

a, b and c reflect the stoichiometry of the linked pro-drug, preferably, a, b and c are a valence of 1^+, 2^+ or 3^+.

For the linked pro-drugs of schemes (1) and (2), above, preferably the NEPi is a monoprotic acid and ARB is a diprotic acid. The angiotensin receptor blocker has a charge of 0, 1 or 2 and the NEPi has a charge of 0 or 1 depending on the pH of the solution, while the overall molecule will be neutral. Ratios of ARB to NEPi will be 1:1, 1:2, 1:3, 3:1, 2:1, 1:1, preferably 1:1, 1:2 or 1:3, most preferably 1:1.

Multi-component salts, particularly with zinc and calcium have been reported in the literature, e.g., *Chem Pharm Bull*, Vol. 53, p. 654 (2005). These ions require a coordination geometry that facilitates the crystallization of multi-component systems. The metal ions have coordinating geometries governed by the atomic orbitals for each species

Valsartan comprises two acidic groupings: the carboxylic acid and the tetrazole. In one embodiment of this aspect of the present invention, the molecular structure of linked pro-drugs of valsartan and a NEPi comprise a linkage between the carboxylic acid and the linking moiety or a linkage between the tetrazole grouping and the linking moiety. In yet another embodiment, the linked pro-drug comprises a trivalent linking moiety linked to the valsartan carboxylic acid grouping, the tetrazole grouping and the NEPi grouping.

In an embodiment of this aspect of the invention, valsartan is linked to (2R,4S)-5-biphenyl-4-yl-4-(3-carboxy-propionylamino)-2-methyl-pentanoic acid ethyl ester by a calcium salt ion.

In a preferred embodiment of the present application, the angiotensin receptor antagonist and the neutral endopeptidase inhibitor are present in a molar ratio of 1:1, 1:2, 1:3, 3:1, 2:1, more preferably 1:1 in the combination as well as in the supramolecular complex. This is also true for the linked pro-drug. Moreover, in the complex, angiotensin receptor antagonist, the neutral endopeptidase inhibitor and the cation are present in a molar ratio of 1:1:1, 1:1:2, 1:1:3, more preferably 1:1:3. This applies equally to the linked pro-drug.

The combination or the dual-acting compound, in particular the complex of the present invention may contain a solvent. This is particularly preferred in the case of the dual-acting compound, in particular the complex, where the solvent may contribute to the intermolecular structure, e.g. the supramolecular interactions. Preferred solvents include water, methanol, ethanol, 2-propanol, acetone, ethyl acetate, methyl-t-butylether, acetonitrile, toluene, and methylene chloride, preferably water. If a solvent is present, one or more molecules per molecule of the active agent can be present. In this case, namely if a stoichiometric amount of the solvent is present, preferably 1, 2, 3, 4 or 5, more preferably 3, molecules of solvent, such as water, can be present per molecule of active agent. Alternatively, the solvent may be present in non-stoichiometric amounts. This means preferably any stoichiometric fraction of the solvent, such as 0.25, 0.5, 0.75, 1.25, 1.5, 1.75, 2.25, 2.5, 2.75, 3.25, 3.5, 3.75, 4.25, 4.5 and 4.75, preferably 2.5, molecules of solvent, such as water, can be present per molecule of active agent. If the dual-acting compound, in particular the complex is in the crystalline form, the solvent may be part of the molecular packing and be trapped in the crystal lattice.

Thus in a preferred embodiment of the present invention, the dual-acting compound, in particular the supramolecular complex is described by the sum formula:

[ARB(NEPi)]$Na_{1-3}.xH_2O$, wherein x is 0, 1, 2 or 3, such as 3, preferably

[ARB(NEPi)]$Na_3.xH_2O$, wherein x is 0, 1, 2 or 3, such as 3, more preferably

[valsartan ((2R,4S)-5-biphenyl-4-yl-4-(3-carboxy-propionylamino)-2-methyl-pentanoic acid ethyl ester)]$Na_3.x H_2O$, wherein x is 0, 1, 2 or 3, such as 3.

Thus in a preferred embodiment of the present invention, the dual-acting compound, in particular the supramolecular complex is described by the sum formula:

[ARB(NEPi)]$Na_{1-3}.xH_2O$, wherein x is 0 to 3, such as 2.5, preferably

[ARB(NEPi)]$Na_3.xH_2O$, wherein x is 0 to 3, such as 2.5, more preferably

[(N-valeryl-N-{[2'-(1H-tetrazole-5-yl)-biphenyl-4-yl]-methyl}-valine) (5-biphenyl-4-yl-4-(3-carboxy-priopionylamino)-2-methyl-pentanoic acid ethyl ester]$Na_3.x H_2O$, in particular [((S)—N-valeryl-N-{[2'-(1H-tetrazole-5-yl)-biphenyl-4-yl]-methyl}-valine) ((2R,4S)-5-biphenyl-4-yl-4-(3-carboxy-propionylamino)-2-methyl-pentanoic acid ethyl ester]$Na_3.x H_2O$, wherein x is 0 to 3, such as 2.5. In this most preferred example, the complex is termed trisodium [3-((1 S,3R)-1-biphenyl-4-ylmethyl-3-ethoxycarbonyl-1-butylcarbamoyl) propionate-(S)-3'-methyl-2'-(pentanoyl{2"-(tetrazol-5-ylate) biphenyl-4'-ylmethyl}amino) butyrate] hemipentahydrate.

A simplified structure of trisodium [3-((1 S,3R)-1-biphenyl-4-ylmethyl-3-ethoxycarbonyl-1-butylcarbamoyl)propionate-(S)-3'-methyl-2'-(pentanoyl{22"-(tetrazol-5-ylate)biphenyl-4'-ylmethyl}amino)butyrate] hemipentahydrate used to formally calculate the relative molecular mass, is shown below.