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July 24, 2024

Re: Docket No. FDA-2022-P-2228

Dear Dr. Platt:

This letter responds to your citizen petition submitted by Hogan Lovells on behalf of Novartis Pharmaceuticals Corporation (Novartis) and received on September 12, 2022 (Petition).[1] Novartis requests that the Food and Drug Administration (FDA or Agency) refrain from approving certain abbreviated new drug applications (ANDAs) that reference Entresto (sacubitril and valsartan) tablets, 24 milligrams (mg);26 mg, 49 mg;51 mg, and 97 mg;103 mg (Entresto) (new drug application (NDA) 207620) as the reference listed drug (RLD). Specifically, the Petition requests that the Agency:

(1) Refrain from approving any ANDA referencing NDA 207620 prior to the February 16, 2024, expiration of Entresto's 3-year exclusivity denoted in FDA's publication *Approved Drug Products With Therapeutic Equivalence Evaluations* (commonly referred to as the Orange Book)[2] with the exclusivity code M-82 (Labeling Revisions Related to Clinical Studies));

(2) Refrain from approving any ANDA referencing NDA 207620 that contains a section viii statement[3] to U.S. Patent Nos. 9,517,226; 9,937,143; and 11,135,192 (each listed in FDA's Orange Book with the patent use code U-3084 (Treatment of Heart Failure With Preserved Ejection Fraction) (HFpEF[4] Patents)) prior to the August 22, 2033, expiration thereof; and

[1] On March 28, 2023, the Agency informed you that it had not yet resolved the issues raised in the Petition because it raised complex issues requiring extensive review and analysis by Agency officials.

[2] Available at https://www.fda.gov/drugs/drug-approvals-and-databases/approved-drug-products-therapeutic-equivalence-evaluations-orange-book.

[3] See section 505(j)(2)(A)(viii) of the Food, Drug, and Cosmetic Act (21 U.S.C. 355(j)(2)(A)(viii)).

[4] Heart failure with preserved ejection fraction.

(3) Refrain from approving any ANDA referencing NDA 207620 that contains a section viii statement to U.S. Patent No. 11,058,667 (listed in the Orange Book with the patent use code U-3170 (Treating Chronic Heart Failure With Reduced Ejection Fraction in Patients Not Taking an ACE [Angiotensin-Converting Enzyme] Inhibitor or an ARB [Angiotensin II Receptor Blocker] or Previously Taking Low Doses of These Agents, by Titrating Up From Half the Usually Recommended Starting Dose) ('667 patent)) prior to the May 9, 2036, expiration thereof.

Novartis previously submitted a citizen petition in 2021 (Docket No. FDA-2021-P-1286) (2021 Petition) requesting that FDA take the same actions as in the Petition. The 2021 Petition was denied with a nonsubstantive response on April 29, 2022.[5]

FDA has carefully considered the information submitted in the Petition, including the Petition's attachments, as well as the administrative record for NDA 207620. For the reasons explained below, we dismiss the first request as moot and deny the second and third requests.[6]

I. LEGAL AND REGULATORY BACKGROUND

A. Drug Approval Pathways Under the Federal Food Drug And Cosmetic Act

Section 505 of the Federal Food, Drug & Cosmetic Act (FD&C Act) (21 U.S.C. 355) establishes approval pathways for three categories of drug applications: (1) 505(b)(1) NDAs, (2) 505(b)(2) NDAs, and (3) 505(j) ANDAs. Because the requests in the 2022 Petition relate to a 505(b)(1) NDA and ANDAs, the remaining discussion will focus primarily on those two pathways.

1. 505(b)(1) NDAs: Stand-Alone Approval Pathway

Section 505(b)(1) of the FD&C Act requires that an application contain, among other things, "full reports of investigations" to show that the drug for which the applicant is seeking approval is safe and effective.[7] NDAs that are supported entirely by investigations either conducted by the applicant or to which the applicant has a right of reference are referred to as *505(b)(1) NDAs* or *stand-alone NDAs*.

[5] Letter from P. Cavazzoni, Director of FDA's Center for Drug Evaluation and Research (CDER), to D. Platt, Novartis, Docket No. FDA-2021-P-1286 (April 29, 2022).

[6] Today, FDA approved an ANDA for sacubitril and valsartan oral tablets, 24 mg;26 mg, 49 mg;51 mg, and 97 mg;103 mg containing section viii statements to the HFpEF Patents.

[7] See section 505(b)(1)(A) of the FD&C Act. A 505(b)(1) NDA must also include: a full list of the articles used as components of the proposed drug; a full statement of the composition of such drug; a full description of the methods used in, and the facilities and controls used for, the manufacture, processing, and packing of such drug; samples of the drug as necessary; proposed labeling for the drug; and pediatric assessments. Id.

FDA will approve a 505(b)(1) NDA if it finds that the information and data provided by the applicant demonstrate that the drug product is safe and effective for the conditions prescribed, recommended, or suggested in the proposed labeling.[8]

2. 505(b)(2) NDAs and ANDAs: Abbreviated Pathways

The Drug Price Competition and Patent Term Restoration Act of 1984 (Hatch-Waxman Amendments)[9] amended the FD&C Act to add sections 505(b)(2) and 505(j) as well as other conforming amendments. These provisions describe abbreviated pathways for 505(b)(2) NDAs and ANDAs, respectively.[10] The Hatch-Waxman Amendments reflect Congress's efforts to balance the need to "make available more low cost generic drugs by establishing a generic drug approval procedure" with new incentives for drug development in the form of exclusivity and patent term extensions.[11] These pathways permit sponsors to rely on what is already known about the previously approved drug, which both allows for a speedier market entry than would be possible with a full, stand-alone 505(b)(1) NDA and leads to increased competition.[12]

Section 505(j) of the FD&C Act establishes an abbreviated approval pathway for a drug that is the same as a previously approved drug (the RLD) with respect to active ingredient; dosage form; route of administration; strength; and, with certain exceptions, labeling and conditions of use.[13] An ANDA applicant also must demonstrate that its proposed drug is bioequivalent to the RLD.[14] An applicant that meets the requirements under section 505(j) for approval may reference the Agency's finding of safety and effectiveness for the RLD and need not repeat the nonclinical and clinical investigations required for approval of an NDA submitted under section 505(b)(1) of the FD&C Act.

B. 3-Year Exclusivity Under the FD&C Act

The Hatch-Waxman Amendments provide incentives for pharmaceutical innovation in the form of exclusivities, including 3-year exclusivity, to protect qualified drugs submitted under section 505(b) of the FD&C Act from competition from certain 505(b)(2) applications and ANDAs for varying periods of time depending on the factual circumstances.

Under section 505(j)(5)(F)(iii) of the FD&C Act and § 314.108(b)(4) (21 CFR 314.108(b)(4)), the Agency will recognize a 3-year period of exclusivity for a drug that contains a previously

[8] See, e.g., section 505(b)(1), (c), and (d) of the FD&C Act and 21 CFR part 314.

[9] Public Law 98-417 (1984).

[10] As the Petition refers only to ANDAs, it is not necessary to discuss the 505(b)(2) pathway here.

[11] See House Report No. 98-857, part 1, at 14–15 (1984), reprinted in 1984 U.S.C.C.A.N. 2647 at 2647–2648.

[12] See *Eli Lilly & Co.* v. *Medtronic, Inc.*, 496 U.S. 661, 676 (1990); see also *Bristol-Meyers Squibb Co. and E.R. Squibb & Sons, Inc.* v. *Royce Labs., Inc.*, 69 F.3d 1130, 1132-34 (Fed. Cir. 1995).

[13] See section 505(j)(2)(A) of the FD&C Act.

[14] Id.

approved active moiety or moieties, when the application contains reports of new clinical investigations (other than bioavailability studies) conducted or sponsored by or on behalf of the applicant that were essential to approval of the application.[15] During this 3-year period, the Agency will not approve an ANDA for the conditions of approval of the original application.

Similarly, FDA will recognize 3-year exclusivity when a supplement to an NDA is approved and the supplement contains reports of new clinical investigations (other than bioavailability studies) conducted or sponsored by or on behalf of the applicant that were essential to approval of the supplement. When a supplement meets the criteria set forth in these provisions, FDA "may not make the approval of an application . . . for a change approved in the supplement effective before the expiration of three years . . . ."[16] Although the statute and regulations use different words to describe 3-year exclusivity for an original NDA (i.e., "conditions of approval") and a supplement to an NDA (i.e., "change approved in the supplement"), FDA has taken a consistent approach to both types of applications in determining their eligibility for 3-year exclusivity and the scope of that exclusivity.[17]

C. Patent Listing Requirements and Patent Certification Requirements

Section 505(b)(1)(A)(viii) of the FD&C Act requires NDA applicants to file as part of the NDA:[18]

> . . . the patent number and expiration date of each patent for which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug, and that — (I) claims the drug for which the applicant submitted the application and is a drug substance (active ingredient) patent or a drug product (formulation or composition) patent; or (II) claims a method of using such drug for which approval is sought or has been granted in the application.

For method of use patents, the information submitted by the NDA applicant and published by FDA includes a brief description of the patented method of use provided by the applicant, known as a *use code*.[19] Upon approval of the NDA, FDA is required to publish patent information submitted under section 505(b)(1) of the FD&C Act[20] and does so in the Orange Book. FDA plays a ministerial role in patent listing and publication of use codes submitted by an NDA

[15] A parallel provision applies 3-year exclusivity to 505(b)(2) NDAs. See section 505(c)(3)(e)(iii) of the FD&C Act.

[16] See sections 505(c)(3)(E)(iv) and 505(j)(5)(F)(iv) of the FD&C Act and § 314.108(b)(5).

[17] See *Otsuka Pharm. Co.* v. *Price*, 869 F.3d 987 (D.C. Cir. 2017).

[18] Section 505(c)(2) of the FD&C Act requires submission of patent information within 30 days of NDA approval. Section 505(c)(2) also imposes an additional patent submission requirement on holders of approved NDAs when those NDA holders subsequently obtain new patent information that could not have been submitted with the NDA.

[19] See § 314.53(c)(2)(ii)(P)(*3*).

[20] Section 505(b)(1), (c)(2), and (j)(7) of the FD&C Act.

applicant for publication in the Orange Book. FDA does not review the applicable patent to evaluate the appropriateness of the NDA applicant's patent listing or the accuracy of its use codes.[21]

The statute also provides that if a patent is issued after NDA approval that covers an approved drug substance, drug product, or method of use of the drug, then the NDA applicant must file certain required patent information with FDA not later than 30 days after the date the patent is issued.[22] FDA's regulations further require that an applicant seeking approval of certain supplements to an approved NDA, including a supplement for a new indication, submit with its supplement information required for a patent that claims the drug substance, drug product, or method of use.[23] Upon approval of the supplement, FDA will publish this patent information in the Orange Book.

The timing of ANDA approval depends on, among other things, relevant patent information listed in the Orange Book for the RLD and whether the ANDA applicant challenges a patent listed in the Orange Book for the RLD (listed patent) or seeks approval for a use covered by a listed method of use patent.[24] For each patent that claims the RLD or a method of using the RLD that the ANDA references and for which the NDA applicant is required to submit information, an ANDA applicant must submit a certification:

> (I) that such patent information has not been filed [a paragraph I certification],
> (II) that such patent has expired [a paragraph II certification],
> (III) of the date on which such patent will expire [a paragraph III certification], or
> (IV) that such patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the new drug for which the application is submitted [a paragraph IV certification] . . . .[25]

An applicant submitting a paragraph IV certification to a listed patent must provide the NDA holder and each patent owner with notice of its patent certification, including a description of the legal and factual basis for the ANDA applicant's assertion that the patent is invalid or not infringed.[26] The purpose of this requirement is "to give notice, if necessary, to the patent holder so that any legal disputes regarding the scope of the patent and the possibility of infringement can be resolved as quickly as possible."[27]

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[21] See, e.g., *Apotex, Inc.* v. *Thompson*, 347 F.3d 1335, 1349 (Fed. Cir. 2003); *aaiPharma Inc.* v. *Thompson*, 296 F.3d 227, 242–243 (4th Cir. 2002).

[22] Section 505(c)(2) of the FD&C Act; § 314.53.

[23] Section 314.53(d)(2).

[24] See 21 CFR 314.107.

[25] Section 505(j)(2)(A)(vii) of the FD&C Act; see also § 314.94(a)(12)(i)(A).

[26] Section 505(j)(2)(B) of the FD&C Act.

[27] *Torpharm, Inc.* v. *Thompson*, 260 F. Supp. 2d 69, 71 (D.D.C 2003), *aff'd*, 354 F.3d 877 (D.C. Cir. 2004).

If a patent is listed at the time an ANDA is submitted, and in response to a paragraph IV certification, the NDA holder or patent owner initiates a patent infringement action against the ANDA applicant within 45 days of receiving the required notice, approval of the ANDA generally will be stayed for 30 months from the date of the notice or such shorter or longer time as the court might order. If the patented drug product qualifies for 5 years of exclusivity and the patent owner, representative, or exclusive patent licensee brings suit for patent infringement during the 1-year period beginning 4 years after the date of approval of the patented drug and within 45 days of receipt of the notice of certification, then the relevant time period before the ANDA may be approved is 7 ½ years from the date of approval of the NDA.[28] When such period has expired, the patent ceases to be a barrier to final ANDA approval, even if the patent litigation is ongoing. Similarly, if the NDA holder and patent owner receive notice of paragraph IV certification and decline to sue within 45 days of receipt of notice, the patent will not be a barrier to ANDA approval.

The FD&C Act provides only one circumstance in which an ANDA applicant need not certify to a listed patent. When a patent is listed in the Orange Book for a method of use, an ANDA applicant seeking to omit that approved method of use covered by the listed patent may submit a *section viii statement* acknowledging that a method of use patent has been listed for the drug but stating that the patent at issue does not claim a use for which the applicant seeks approval. Specifically, section 505(j)(2)(A)(viii) of the FD&C Act provides that:

> . . . if with respect to the listed drug referred to in [section 505(j)(2)(A)(i) of the FD&C Act] information was filed under subsection (b) or (c) for a method of use patent which does not claim a use for which the applicant is seeking approval under this subsection, [the ANDA must contain] a statement that the method of use patent does not claim such a use.

Submission of a section viii statement requires the ANDA applicant to omit from its labeling information pertaining to the protected use, sometimes colloquially referred to as a carve out. In determining the propriety of a labeling carve out under this section, consistent with its ministerial role, FDA compares the patent information provided by the NDA applicant with the drug's approved labeling and determines whether a drug with the patented use carved out remains safe and effective for the remaining nonprotected conditions of use. If FDA determines that such differences in labeling would render the ANDA drug less safe or effective than the RLD for all remaining, nonprotected conditions of use, the ANDA applicant must address the patent(s) by submitting a certification described in section 505(j)(2)(A)(vii) of the FD&C Act.[29] Thus, if an ANDA applicant files a section viii statement (and proposes labeling that does not seek approval for the protected use), and FDA determines that any differences between the proposed ANDA labeling and the RLD labeling do not render the ANDA drug less safe or effective than the RLD for all remaining, nonprotected conditions of use, the patent(s) claiming the protected method of use will not serve as a barrier to ANDA approval.[30] Under the FD&C Act, an ANDA applicant

[28] Section 505(j)(5)(B)(iii) and (j)(5)(F)(ii) of the FD&C Act and § 314.107(b)(3)(i)(B).

[29] See also § 314.94(a)(12)(i)(A).

[30] See section 505(j)(2)(A)(viii) of the FD&C Act; and § 314.127(a)(7).

must submit either a patent certification or a section viii statement for each listed patent for the RLD.[31]

D. Labeling Requirement for Products Approved as ANDAs

Section 505(j)(2)(A)(i) of the FD&C Act requires that an ANDA contain "information to show that the conditions of use prescribed, recommended, or suggested in the labeling proposed for the new drug have been previously approved for a [listed drug] . . . ." Also, section 505(j)(2)(A)(v) of the FD&C Act requires that an ANDA contain:

> . . . information to show that the labeling proposed for the new [generic] drug is the same as the labeling approved for the listed drug . . . except for changes required because of differences approved under a petition filed under [section 505(j)(2)(C) of the FD&C Act] or because the new [generic] drug and the listed drug are produced or distributed by different manufacturers.

A parallel provision appears in section 505(j)(4)(G) of the FD&C Act.[32]

Although the requirements set forth in sections 505(j)(2)(A)(v) and 505(j)(4)(G) of the FD&C Act are known as the *same labeling* requirements, they do not require that a generic drug's labeling be identical to that of the listed drug it references in every respect. Instead, these provisions reflect, among other things, Congress's intent that the generic drug be safe and effective for each condition of use prescribed, recommended, or suggested in the generic drug labeling without requiring that an ANDA be approved for each condition of use for which the listed drug is approved. In describing the Hatch-Waxman Amendments, Congress explicitly acknowledged that "the bill permits an ANDA to be approved for less than all of the indications for which the listed drug has been approved."[33]

In interpreting the statutory exception to the same labeling requirement, which allows certain labeling differences because the proposed ANDA and the listed drug are "produced or distributed by different manufacturers," among other things, the regulations at § 314.92(a)(1) explicitly state that a proposed generic drug product must have the same conditions of use as the listed drug, except that "conditions of use for which approval cannot be granted *because of exclusivity or an existing patent may be omitted*" (emphasis added).

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[31] See section 505(j)(2)(A)(vii) through (viii) of the FD&C Act.

[32] Section 505(j)(4)(G) of the FD&C Act provides that FDA shall approve an ANDA unless, among other things, the "information submitted in the application is insufficient to show that the labeling proposed for the drug is the same as the labeling approved for the listed drug . . . except for changes required because of differences approved under [section 505(j)(2)I of the FD&C Act, in an ANDA suitability petition] or because the drug and the listed drug are produced or distributed by different manufacturers."

[33] House Report No. 98-857, pt. 1, at 2 (1984); see also at 21 ("The [ANDA] applicant need not seek approval for all of the indications for which the listed drug has been approved.").

Similarly, § 314.94(a)(8)(iv)) sets forth some examples of permissible differences in labeling that may result because the generic drug product and listed drug are produced or distributed by different manufacturers. Permissible differences include, but are not limited to, the following:

> . . . differences in expiration date, formulation, bioavailability, or pharmacokinetics, labeling revisions made to comply with current FDA labeling guidelines or other guidance, or omission of an indication or other aspect of labeling protected by patent or accorded exclusivity under section 505(j)(5)(F) of the [FD&C Act].[34]

The regulations at § 314.127(a)(7) further provide that, to approve an ANDA containing proposed labeling that omits "aspects of the listed drug's labeling [because those aspects] are *protected by patent, or by exclusivity*," we must find that the "differences do not render the proposed drug product less safe or effective than the listed drug for all remaining, nonprotected conditions of use" (emphasis added). In practice, when determining how to carve out language from an ANDA's labeling to give effect to the RLD's patent- or exclusivity -protection, the current labeling of the RLD is examined and any appropriate omissions of patent- or exclusivity-protected information are made. It then determines whether the labeling with the protected information carved out remains safe and effective for the remaining nonprotected conditions of use. Thus, starting with the currently approved labeling for the RLD, these provisions specifically affirm that ANDA applicants may carve out from their proposed labeling any patent- or exclusivity-protected indication or other aspect of labeling and obtain approval for the remaining nonprotected conditions of use as long as the ANDA remains safe and effective for the remaining nonprotected conditions of use.

Relevant case law affirms an ANDA applicant's ability to carve out protected labeling without violating the same labeling requirement. For example, in *Bristol-Myers Squibb Co.* v. *Shalala*, 91 F.3d 1493 (D.C. Cir. 1996), the Washington D.C. Circuit Court ruled that "the statute expresses the legislature's concern that the new generic be safe and effective for each indication that will appear on its label; whether the label for the new generic lists every indication approved for use of the pioneer is a matter of indifference."[35] Similarly, in *Sigma-Tau Pharmaceuticals, Inc.* v. *Schwetz*, 288 F.3d 141 (4th Cir. 2002), the Fourth Circuit upheld the right of an ANDA applicant to carve out an indication protected by orphan drug exclusivity as a permissible difference due to a difference in manufacturer.[36] Sigma-Tau Pharmaceuticals, Inc. (Sigma-Tau) argued that FDA was obligated to look beyond the labeling an ANDA applicant proposed to use in determining whether a generic drug would violate an innovator's exclusivity protection. The court stated that Sigma-Tau's argument would extend exclusivity beyond what Congress intended and "frustrate the longstanding practice of Congress, the FDA, and the courts not to

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[34] Section 314.94(a)(8)(iv). We note that although the regulation provides removal of an aspect of labeling protected by exclusivity under section 505(j)(5)(F) of the FD&C Act as an example of a permissible difference due to difference in manufacturer, FDA has never interpreted this example as the only permissible exclusivity-based carve out.

[35] *Bristol-Myers Squibb Co.* v. *Shalala*, 91 F.3d 1493, 1500 (D.C. Cir. 1996). See also *Spectrum Pharm., Inc.* v. *Burwell*, 824 F.3d 1062, 1066 (D.C. Cir. 2016) (explaining that D.C. Circuit has "approved FDA's general approach to labeling carve outs as an acceptable interpretation of the [FD&C Act]" and upholding FDA's approval of a generic drug with an indication protected by orphan exclusivity carved out).

[36] *Sigma-Tau Pharms., Inc.* v. *Schwetz*, 288 F.3d 141, 148, n. 3 (4th Cir. 2002).

interfere with physicians' judgments and their prescription of drugs for off-label uses."[37] The court reasoned that "[Sigma-Tau's theory] to bar the approval of generic drugs, even for unprotected indications. . . . [would add] a huge evidentiary hurdle to the generic drug approval process [and] would be profoundly anti-competitive."[38] Accordingly, the court rejected Sigma-Tau's argument and concluded that the statutory scheme permitted an ANDA applicant to carve out the exclusivity-protected indication at issue.

Consistent with §§ 314.94(a)(8) and 314.127(a)(7), the Agency may approve an ANDA with labeling that differs from the listed drug labeling because aspects of the listed drug labeling are protected by patent or exclusivity.[39]

Thus, the statute, regulations, and applicable case law permit the omission of an indication or other aspect of labeling protected by a listed patent or applicable exclusivity as an acceptable difference between the proposed generic drug and the RLD that are produced or distributed by different manufacturers if the omission does not render the proposed generic drug less safe or effective than the RLD for the nonprotected conditions of use that remain in the labeling.

II. BACKGROUND

A. Heart Failure

Heart failure (HF) is not a well-defined disease; rather, HF is a complex clinical syndrome characterized by typical symptoms (e.g., shortness of breath, lower extremity swelling, fatigue) that may be accompanied by signs (e.g., elevated jugular venous pressure, pulmonary crackles, peripheral edema) caused by a structural and/or functional cardiac abnormality, resulting in a reduced cardiac output and/or elevated intracardiac pressures at rest or during stress.[40] From a traditional pathophysiological viewpoint, HF can be thought of as a syndrome that occurs when the heart's output is inadequate to meet the body's needs (or adequate only at the cost of high

[37] Id. (citations omitted).

[38] Id. Also *Bristol-Myers Squibb Co.* v. *Shalala*, 91 F.3d at 1500; *AstraZeneca Pharms.* v. *FDA*, 872 F. Supp. 2d 60, 89 (D.D.C. 2012).

[39] Such differences may include, but are not limited to, omissions of words or phrases from the RLD's labeling and minor attendant changes to ensure that the language of the labeling reads properly. Letter from J. Woodcock, Director of FDA's CDER, to J Rodenberg, Teva Pharmaceuticals, Docket No. FDA-2015-P-3980 at 14–15 (March 24, 2016).

[40] See, e.g., Entresto Supplement 018 Clinical Reviews(s) at 20 (PDF 51/176), available at https://www.accessdata.fda.gov/drugsatfda_docs/nda/2021/207620Orig1s018.pdf (citing Ponikowski P, et al., ESC Scientific Document Group, 2016 ESC Guidelines for the Diagnosis and Treatment of Acute and Chronic Heart Failure: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure of the European Society of Cardiology (ESC) Developed With the Special Contribution of the Heart Failure Association (HFA) of the ESC, European Heart Journal, 2016, 37(27):2129–2200); see also Heidenreich PA, Bozkurt B, Aguilar D, et al., 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines, Circulation, 2022, 145(18):e895–e1032.

filling pressures).[41] HF can be chronic and is associated with premature mortality and significant morbidity, largely due to high rates of hospitalization for HF.[42] It has been reported that HF affects over 6.2 million American adults, with an incidence approaching 21 per 1,000 population after the age of 65 years.[43] HF is the leading cause of hospital admissions in patients over the age of 65 years in the United States where there has been an increase in this trend over the last 2 decades.[44] HF affects more than 64 million people worldwide, and attempts to decrease its social and economic burden have become a major global public health priority.[45]

There are at least four distinct mechanisms leading to HF, generally involving failures in cardiac valves, increased load against which the heart pumps, systolic dysfunction, and diastolic dysfunction.[46] Each mechanism represents a fundamentally different form of HF from the others. For example, systolic dysfunction, or the impairment of the heart's ability to contract (i.e., pump out/eject blood), is a fundamentally different form of HF than diastolic dysfunction, or the impairment of the heart's ability to relax (i.e., fill up with blood).[47] There are multiple mechanisms that can result in either systolic dysfunction or diastolic dysfunction, and patients can have multiple mechanisms resulting in their HF syndrome.[48]

Understanding which mechanism or mechanisms are likely causing the symptoms of HF in any particular patient is important to a clinician's diagnosis and treatment considerations.[49] There

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[41] See, e.g., Pfeffer MA, Shah AM, Borlaug BA, Heart Failure With Preserved Ejection Fraction in Perspective, Circ Res, 2019, 124(11):1598–1617 (citing Braunwald E. Heart Disease: A Textbook of Cardiovascular Medicine. 4th ed. Philadelphia, WB: Saunders; 1992).

[42] See, e.g., Dunlay SM, Roger VL, Redfield MM, Epidemiology of Heart Failure With Preserved Ejection Fraction, Nat Rev Cardiol, 2017, 14(10):591–602 (footnotes omitted).

[43] Lauren K. Truby, Joseph G. Rogers, Advanced Heart Failure: Epidemiology, Diagnosis, and Therapeutic Approaches, JACC: Heart Failure, 2020, 8(7):523–536.

[44] Agarwal MA, Fonarow GC, Ziaeian B, National Trends in Heart Failure Hospitalizations and Readmissions From 2010 to 2017, JAMA Cardiol, 2021, 6:952–956.

[45] Savarese G, Becher PM, Lund LH, Seferovic P, Rosano GMC, Coats AJS, Global Burden of Heart Failure: A Comprehensive and Updated Review of Epidemiology, Cardiovasc Res, 2023, 118(17):3272–3287.

[46] See, e.g., Ponikowski P, et al., ESC Scientific Document Group, 2016 ESC Guidelines for the Diagnosis and Treatment of Acute and Chronic Heart Failure: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure of the European Society of Cardiology (ESC) Developed With the Special Contribution of the Heart Failure Association (HFA) of the ESC, European Heart Journal, 2016, 37(27):2129–2200, 2136–17).

[47] See, e.g., Tromp J, Westenbrink BD, Ouwerkerk W, van Veldhuisen DJ, Sarnani NJ, Ponikowski P, Metra M, Anker SD, Cleland JG, Dickstein K, Filippatos G, van der Harst P, Lang CC, Ng LL, Zannad F, Zwinderman AH, Hillege HL, van der Meer P, Voors AA, Identifying Pathophysiological Mechanisms in Heart Failure With Reduced Versus Preserved Ejection Fraction, J Am Coll Cardiol, 2018, 72:l081–1090.

[48] See, e.g., Schwinger RHG, Pathophysiology of Heart Failure, Cardiovasc Diagn Ther, 2021, 11(1):263–276, 263, doi: 10.21037/cdt-20-302. PMID: 33708498; PMCID: PMC7944197.

[49] See, e.g., Ponikowski P, et al., ESC Scientific Document Group, 2016 ESC Guidelines for the Diagnosis and Treatment of Acute and Chronic Heart Failure: The Task Force for the Diagnosis and Treatment of Acute and

may be a few special cases and secondary mechanisms to consider, but most drugs that have benefits in HF work in the setting of impaired contraction (i.e., systolic disfunction) and have immediate benefits likely derived through reducing the load against which the damaged muscular layer of the heart has to work.

1. Classification of HF Based on Left Ventricular Ejection Fraction

Left ventricular ejection fraction (LVEF) is one of many measures of cardiac performance used in clinical practice to diagnosis and treat patients with chronic HF. LVEF is an indirect measure (often obtained using echocardiography) of global left ventricular systolic function and represents the proportion of blood ejected during left ventricular systole. More specifically, LVEF measures what fraction of the blood that fills the left ventricle during diastole is ejected/pumped during systole. The American Society of Echocardiography (ASE) defines normal mean LVEF ± standard deviation (SD) (2-SD range) as 62 ± 5% (52–72) in males and 64 ± 5% (54–74) in females.[50] When a patient's LVEF is below normal, there is impaired contraction of the heart (i.e., systolic disfunction).

Historically, HF has been classified based on LVEF as either (1) HF with reduced ejection fraction (commonly referred to as HFrEF) or (2) HF with preserved ejection fraction (commonly referred to as HFpEF).[51] Although the origin of the term HFpEF is vague, the original intent of this term was to differentiate HF in which the mechanism for contraction was impaired (i.e., systolic dysfunction)—as evidenced by a below normal LVEF—from HF more likely to represent impaired relaxation (i.e., diastolic dysfunction).[52] In other words, the terms HFrEF and HFpEF were long understood as representing fundamentally distinct forms of HF.[53] In the 1980s and 1990s, however, the diagnosis of HF became synonymous with the presence of "reduced LVEF" largely because of the advent of major randomized clinical trials designed to study HF patients with impaired contraction and having a primary endpoint of mortality.[54] Many of those

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Chronic Heart Failure of the European Society of Cardiology (ESC) Developed With the Special Contribution of the Heart Failure Association (HFA) of the ESC, European Heart Journal, 2016, 37(27):2129–2200, 2136–17); see also Schwinger RHG, Pathophysiology of Heart Failure, Cardiovasc Diagn Ther, 2021, 11(1):263–276, 263, doi: 10.21037/cdt-20-302. PMID: 33708498; PMCID: PMC7944197.

[50] See Entresto Supplement 018 Clinical Review(s) at 20 (PDF 51/176) (citing Lang RM, Badano LP, Mor-Avi V, et al., Recommendations for Cardiac Chamber Quantification by Echocardiography in Adults: An Update From the American Society of Echocardiography and the European Association of Cardiovascular Imaging, J Am Soc Echocardiogr, 2015, 28:1–39.e14).

[51] See, e.g., Bozkurt B, et al., Universal Definition and Classification of Heart Failure: A Report of the Heart Failure Society of America, Heart Failure Association of the European Society of Cardiology, Japanese Heart Failure Society and Writing Committee of the Universal Definition of Heart Failure, J of Cardiac Fail, 2021, 27(4):387, 392.

[52] See, e.g., Cleland JGF, Pellicori P, Defining Diastolic Heart Failure and Identifying Effective Therapies, JAMA, 2013, 309(8):825–826, 825, doi: 10.1001/jama.2013.1569.

[53] See, e.g., Lam CSP, et al., Classification of Heart Failure According to Ejection Fraction, J Am Coll Cardiol, 2021, 77(25):3217–25, 3219.

[54] See, e.g., Lam CSP, et al., Classification of Heart Failure According to Ejection Fraction, J Am Coll Cardiol, 2021, 77(25):3217–25, 3218–19.

studies employed a cutoff for LVEF as an exclusion criterion, typically excluding from the trial HF patients with LVEF greater than 35 percent to 40 percent (or sometimes greater than 45 percent). This cutoff was driven by various factors, including interest in having a high enough rate of mortality and hospitalization to make the studies feasible, **but it was not based on a comprehensive inclusion of all patients with impaired contraction** (i.e., patients presenting within the full range of *reduced* LVEF).[55] Studies typically used cutoffs of 40 percent or 45 percent, because they had similar interests in enrichment and because this exclusion criterion cutoff got incorporated into resulting published guidelines as *HF with reduced ejection fraction* or HFrEF. The term HFrEF then came to be widely understood as HF with LVEF less than 40 percent or less than 45 percent (based on cutoffs used in many studies). Accordingly, various HF treatments (including Entresto upon its initial approval) have been approved with indications relating to HF and reduced ejection fraction, which is understood by clinicians as conveying both the setting in which the drug was studied (i.e., impaired contraction) and the range of baseline LVEF measurements over which the drug had been studied (likely LVEF less than 40 percent).

In contrast to HFrEF, the origin of the clinical entity HF with preserved ejection fraction or HFpEF is vague,[56] and proffered definitions of the condition continue to evolve.[57] As noted, the original intent of the term HFpEF was to differentiate HF in which the mechanism for contraction was impaired from HF more likely to represent impaired relaxation.[58] But the enrichment strategy described above of excluding HF patients with LVEF greater than 35 percent to 45 percent from HF trials led to an evidence void for therapies effective in patients with LVEF greater than 40 percent, who were then arbitrarily grouped by published guidelines and others under the term HFpEF. Generally, anything above the HFrEF range became known as HFpEF or, perhaps, also arbitrarily, HF with mildly reduced (or sometimes, *mid-range*) EF ("HFmrEF"). Clinical trials have employed various LVEF cutoffs such as LVEF greater than or equal to 40 percent or greater than or equal to 45 percent or greater than or equal to 50 percent, and some purport to define a HFpEF population based on such inclusion criteria.[59] In addition, published guidelines have offered inconsistent definitions for HFpEF, some of which have changed over time, and some guidelines have also introduced new terms for classifying HF based on LVEF (e.g., HFmrEF).[60] Despite its vague origins and controversial definition(s) that

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[55] See, e.g., 3 Pfeffer MA, Shah AM, Borlaug BA, Heart Failure With Preserved Ejection Fraction In Perspective, Circ Res, 2019, 124(11):1598–1617, 1600–1601, doi: lO 1161/CIRCRESAHA119.313572 (footnotes omitted).

[56] See Borlaug BA, Paulus WJ, Heart Failure With Preserved Ejection Fraction: Pathophysiology, Diagnosis, and Treatment, Eur Heart J, 2011, 32(6):670–679.

[57] See, e.g., Dunlay S, Roger V, Redfield M, Epidemiology of Heart Failure With Preserved Ejection Fraction, Nat Rev Cardiol, 2017, 14:591–602, 591.

[58] See, e.g., Cleland JGF, Pellicori P, Defining Diastolic Heart Failure and Identifying Effective Therapies, JAMA, 2013, 309(8):825–826, 825, doi: 10.1001/jama.2013.1569.

[59] See Fonarow GC, Stough WG, Abraham WT, Albert NM, Gheorghiade M, Greenberg BH, et al., Characteristics, Treatments, and Outcomes of Patients With Preserved Systolic Function Hospitalized for Heart Failure: A Report From the OPTIMIZE-HF Registry, J Am Coll Cardiol, 2007, 50(8):768–77, 769.

[60] See Entresto Supplement 018 Clinical Review(s) at 21 (PDF 52/176) ("In 2013, the [American College of Cardiology and American Heart Association (ACCF/AHA)] guidelines classified HF based on LVEF as HFrEF

continue to evolve, HF with preserved ejection fraction or HFpEF is considered in clinical practice to be a chronic condition of the HF syndrome associated with significant morbidity and mortality.[61] While HFpEF is associated with several comorbidities that somewhat overlap with those observed in HFrEF, no well-defined parameter has been established to demarcate HFpEF from HFrEF, but distinct ventricular structural and cellular deviations have been observed that indicate distinct mechanisms for HFpEF and HFrEF.[62]

In light of what is currently known (and unknown) about the clinical entity HFpEF, the definition of HFpEF remains controversial and continues to evolve.[63] Currently, there is no FDA-approved treatment effective specifically for the entire population that could reasonably be described as patients with HFpEF. Nonetheless, as noted above, HFpEF is a chronic condition that is associated with significant morbidity and mortality. Clinical trials of drugs approved to treat patients with HFrEF, such as angiotensin receptor blockers, ACE inhibitors, and beta blockers have not demonstrated efficacy in the entire population of patients who could be categorized within prevailing definitions of HFpEF. In clinical practice, patients with HFpEF tend to receive treatment for their comorbidities such as hypertension, diabetes mellitus, obesity, sleep apnea, etc., and diuretics to treat fluid overload.

2. Pitfalls of the Classification of HF Based on Strict LVEF Cutoff Points

First, as described above in section II.A.1, the foundation of HF classification based on LVEF as described above is shaky. Second, the most common modality used to measure LVEF, two-dimensional echocardiography, can have up to 10 percent inter- and intra-observer and temporal

when LVEF ≤ 40%, HFpEF when LVEF ≥ 50%, HFpEF borderline when LVEF is 41 to 49%, and HFpEF improved when LVEF > 40% in patients who previously had HFrEF. In 2016, the European Society of Cardiology (ESC) Guidelines for the diagnosis and treatment of acute and chronic heart failure reclassified patients with HF with LVEF 40–49%, from HFpEF described in [prior] guidelines to HF with mid-range ejection fraction (HFmrEF). The proposed rationale to categorize patients based on LVEF was the difference in the prevalence of underlying etiologies, demographics, co-morbidities, and response to therapies such as angiotensin converting enzyme inhibitors (ACE[i]), ARB, mineralocorticoid receptor antagonists (MRA) and beta blockers based on LVEF. The ESC guidelines also state that, 'identifying *HFmrEF as a separate group will stimulate research into the underlying characteristics, pathophysiology and treatment of this group of patients. Patients with HFmrEF most probably have primarily mild systolic dysfunction, but with features of diastolic dysfunction.*'" (emphasis added in clinical review; citations omitted)).

[61] See, e.g., Roger, V, Epidemiology of Heart Failure: A Contemporary Perspective, Circulation Research, 2021, 128 (10):1421–1434, 1423–24, doi: 10.1161/CIRCRESAHA.121.318172.

[62] See, e.g., Entresto Supplement 018 Clinical Review(s) at 22–23 (PDF 53-54/176) (citing Oktay AA, Rich JD, Shah SJ, The Emerging Epidemic of Heart Failure With Preserved Ejection Fraction, Curr Heart Fail Rep, 2013, 10:401–410; and Borlaug BA, Redfield MM, Diastolic and Systolic Heart Failure Are Distinct Phenotypes Within the Heart Failure Spectrum, Circulation, 2011, 123(18):2006–13; discussion 2014).

[63] See, e.g., Roger, V, Epidemiology of Heart Failure: A Contemporary Perspective, Circulation Research, 2021, 128(10):1421–1434, 1423, doi: 10.1161/CIRCRESAHA.121.318172, (citations omitted) (noting controversy surrounding HFpEF).

variability in assessment of LVEF depending on the technique(s) used.[64] Hence, there can be a significant overlap between patients with LVEF less than 40 percent and greater than or equal to 45 percent. Third, LVEF can change over time depending on loading conditions. Fourth, patients with normal LVEF may still have abnormal systolic function as measured by global longitudinal strain or mid-wall fractional shortening and ejection fraction.[65] Hence, a normal LVEF is not synonymous with normal left ventricular systolic function.

B. Entresto (Sacubitril and Valsartan) Tablets

On July 7, 2015, FDA approved Novartis's NDA 207620 for Entresto (sacubitril and valsartan) tablets, 24 mg;26 mg, 49 mg;51 mg, and 97mg;103 mg. Entresto was originally approved for the following adult HF indication.

> **1.1 Adult Heart Failure**
> Entresto is indicated to reduce the risk of cardiovascular death and hospitalization for heart failure in patients with chronic heart failure (NYHA Class II–IV) and reduced ejection fraction.
>
> Entresto is usually administered in conjunction with other heart failure therapies, in place of an ACE inhibitor or other ARB.[66,67]

To support approval of Entresto's original 505(b)(1) application, Novartis conducted a single-phase 3 clinical trial referred to as *PARADIGM-HF* (PARADIGM).[68] PARADIGM was a multinational, randomized, double-blind trial comparing Entresto and enalapril in adult patients

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[64] See Thavendiranathan P, Grant AD, Negishi T, Plana JC, Popović ZB, Marwick TH, Reproducibility of Echocardiographic Techniques for Sequential Assessment of Left Ventricular Ejection Fraction and Volumes: Application to Patients Undergoing Cancer Chemotherapy, J Am Coll Cardiol, 2013, 61(1):77–84; see also Pellikka PA, She L, Holly TA, et al., Variability in Ejection Fraction Measured by Echocardiography, Gated Single-Photon Emission Computed Tomography, and Cardiac Magnetic Resonance in Patients With Coronary Artery Disease and Left Ventricular Dysfunction, JAMA Netw Open, 2018, 1(4):e181456.

[65] See Entresto Supplement 018 Clinical Review(s) at 22 (PDF 53/176) (citing Yu CM, Lin H, Yang H, Kong SL, Zhang Q, Lee SW, Progression of Systolic Abnormalities in Patients With "Isolated" Diastolic Heart Failure and Diastolic Dysfunction, Circulation, 2002, 105:1195–1201; and Borlaug BA, Lam CS, Roger VL, Rodeheffer RJ, Redfield MM, Contractility and Ventricular Systolic Stiffening in Hypertensive Heart Disease Insights into the Pathogenesis of Heart Failure With Preserved Ejection Fraction, J Am Coll Cardiol, 2009, 54(5):410–8.

[66] See Original Entresto Labeling (Rev. 7/2015), available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/207620Orig1s000lbl.pdf.

[67] On October 1, 2019, Novartis obtained approval of its efficacy supplement sNDA 207620/S-013, which provided for the use of Entresto in the following indication in pediatric patients: "for the treatment of symptomatic heart failure with systemic left ventricular systolic dysfunction in pediatric patients aged one year and older. Entresto reduces NT-proBNP and is expected to improve cardiovascular outcomes." This is reflected in a different subsection (1.2) of the INDICATIONS AND USAGE section of Entresto's prescribing information.

[68] See, e.g., Entresto 2015 Summary Review at 8 (PDF 9/31), available at https://www.accessdata.fda.gov/drugsatfda_docs/nda/2015/207620Orig1s000SumR.pdf.

with symptomatic chronic HF (NYHA class II–IV) and systolic dysfunction.[69] The design of PARADIGM employed various inclusion criteria, including that the study population consist of chronic HF patients who presented with a baseline measurement of LVEF less than or equal to 35 percent.[70] PARADIGM demonstrated that Entresto, a combination of a neprilysin inhibitor (sacubitril) and a renin-angiotensin system (RAS) inhibitor (valsartan), was superior to a RAS inhibitor (enalapril), in reducing the risk of the combined endpoint of cardiovascular death or hospitalization for HF, based on a time-to-event analysis.[71]

1. Entresto's Important Adverse Reactions and Subsection 2.6[72] Dose Adjustment for Patients Not Taking an ACE Inhibitor or ARB or Previously Taking Low Doses of These Agents

As noted, Entresto (sacubitril and valsartan) is a combination of a neprilysin inhibitor and an ARB (i.e., a RAS inhibitor), respectively. The safety review for Entresto's original approval focused on characterizing the risk of angioedema and the other known class adverse reactions of RAS inhibitors, including hypotension, renal impairment and hyperkalemia.[73] PARADIGM and two supportive phase 2 studies, including one referred to as "TITRATION," served as the primary sources of safety data for Entresto's original NDA submission.[74]

All subjects in PARADIGM were on an ACE inhibitor (ACEi) or ARB at screening before entering a single-blind run-in period, and therefore, PARADIGM did not provide information regarding the tolerability of Entresto or appropriate titration for patients who are ACEi- or ARB-naïve or on lower doses of these agents at baseline.[75] Novartis proposed to recommend a starting dose for Entresto of 50 mg twice daily for patients who are ACEi- or ARB-naïve or on lower doses at baseline.[76] To inform the proposed titration regimen for Entresto, Novartis conducted a

[69] See Entresto Labeling (Rev. 4/2024), subsection 14.1, available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/218591Orig1s000,%20207620Orig1s025lbl.pdf.

[70] See Entresto 2015 Summary Review at PDF 9/31 ("PARADIGM-HF was an . . . active-controlled trial . . . in 8,442 patients age ≥ 18 with NYHA class II to IV chronic heart failure and an LVEF ≤ 40% (≤ 35% per protocol amendment 1)).

[71] See Entresto Labeling (Rev. 4/2024), subsection 14.1 ("(hazard ratio 0.80; 95% confidence interval, 0.73, 0.87, p < 0.0001)") available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/218591Orig1s000,%20207620Orig1s025lbl.pdf.

[72] While the Petition's discussion of the modified dosing regimen protected by the '667 patent refers to "[s]ection 2.5," the Entresto labeling has since been updated, and the modified dosing regimen protected by the '667 patent is now described in subsection 2.6 of the current labeling.

[73] Entresto 2015 Clinical Review at 77 (PDF 77/171). See also at 11 (PDF 11/171) ("The important risks identified during the safety review are angioedema, hypotension, renal impairment, and hyperkalemia.").

[74] See Entresto 2015 Clinical Review at 82 (PDF 82/171).

[75] See Entresto 2015 Medical Review(s) at 69 (PDF 81/299), available at https://www.accessdata.fda.gov/drugsatfda_docs/nda/2015/207620Orig1s000MedR.pdf.

[76] Entresto 2015 Medical Review(s) at 69 (PDF 81/299).

phase II safety and tolerability study referred to as "TITRATION," which was a 3-month, randomized, double-blind comparison of two different upward dose titration regimens in 498 subjects with HF and with moderate to severely reduced/abnormal LVEF.[77] TITRATION evaluated two titration schemes, both using the target dose of 200 mg twice daily. All subjects in TITRATION received open-label Entresto, 50 mg twice daily during a run-in phase of approximately 1 week.[78] Patients were randomized to one of the following two treatment arms in a 1:1 ratio in a double-blind manner: (1) conservative up-titration: Entresto was up-titrated from 50 mg twice daily to 200 mg twice daily over 6 weeks (including the run-in phase) and (2) condensed up-titration: Entresto was up-titrated from 100 mg twice daily to 200 mg twice daily over 3 weeks (including the run-in phase).[79] FDA determined that the results of TITRATION showed that Entresto was well tolerated in terms of the commonly observed adverse reactions such as hypotension, hyperkalemia, and renal dysfunction following either a condensed or conservative up-titration regimens to achieve the target dose of 200 mg twice daily.[80] FDA also determined that "[p]atients who were ACEi/ARB naïve or taking lower pre-study doses of ACEis/ARBs (low RAS stratum) were better able to achieve and maintain the target dose of [Entresto] 200 mg BID if they were up-titrated more gradually, whereas the rate of up-titration was less important in patients who were taking higher pre-study doses of ACEis/ARBs (high [renin-angiotensin-aldosterone system] RAAS stratum)."[81] FDA also found that the incidence of hyperkalemia was relatively higher with the condensed titration scheme for both strata.[82] The Agency concluded that Novartis's "proposed titration scheme seems reasonable," and that "[a] longer titration period with a starting dose of 50 mg [twice daily] may reduce the risk of hypotension, renal impairment and hyperkalemia in patients previously on a low dose of an ACEi or ARB."[83]

Subsection 2.6 of Entresto's prescribing information provides a modified dosing regimen informed by the TITRATION study for patients not taking an ACE inhibitor or ARB or previously taking low doses of these agents:

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[77] See Entresto 2015 Medical Review(s) at 69 (PDF 81/299); see also at 27 (PDF 39/299).

[78] Entresto 2015 Medical Review(s) at 69 (PDF 81/299).

[79] See Entresto 2015 Clinical Pharmacology and Biopharmaceutics Review(s) at 16 (PDF 24/53), available at https://www.accessdata.fda.gov/drugsatfda_docs/nda/2015/207620Orig1s000ClinPharmR.pdf.

[80] See Entresto 2015 Clinical Pharmacology and Biopharmaceutics Review(s) at 16 (PDF 24/53).

[81] Entresto 2015 Clinical Pharmacology and Biopharmaceutics Review(s) at 16 (PDF 24/53).

[82] See Entresto 2015 Clinical Pharmacology and Biopharmaceutics Review(s) at 16 (PDF 24/53).

[83] Entresto 2015 Medical Review(s) at 70 (PDF 82/299) (emphasis added); see also at 80 (PDF 92/299) ("The results of the phase 2 dose regimen study (TITRATION) suggests that patients who were previously on low dose of ACEi and ARBs ***might*** benefit from a slow up-titration regimen (a 6-week regimen) rather than a fast up-titration regimen (a 3-week regimen) to increase tolerability and reduce the risk of adverse events such as hypotension, hyperkalemia and renal impairment. We agree with the proposed titration strategy from a safety perspective" (emphasis added).); but see Entresto 2015 Clinical Pharmacology and Biopharmaceutics Review(s) at 17 (PDF 25/53) ("The TITRATION study was relatively small but supports the proposed dose titration scheme for [Entresto]. . . . Patients who are naïve to ACE inhibitors/ARBs or are taking low doses of these drugs should use a lower starting dose (50 mg BID) of [Entresto].").

> **2.6 Dose Adjustment for Patients Not Taking an ACE inhibitor or ARB or Previously Taking Low Doses of These Agents**
> In patients not currently taking an ACE inhibitor or an angiotensin II receptor blocker (ARB) and for patients previously taking low doses of these agents, start [Entresto] at half the usually recommended starting dose. After initiation, increase the dose every 2 to 4 weeks in adults and every 2 weeks in pediatric patients to follow the recommended dose escalation thereafter *[see Dosage and Administration (2.2, 2.3)]*.
>
> Note: Initiate pediatric patients weighing 40 to 50 [kilograms] kg who meet this criterion at 0.8 mg/kg twice daily using the oral suspension *[see Dosage and Administration (2.3, 2.4)]*.

In addition, section 5 of Entresto's prescribing information includes, among others, the following warnings and precautions concerning Entresto's important adverse reactions:

> **5.3 Hypotension**
> [Entresto] lowers blood pressure and may cause symptomatic hypotension [*see Adverse Reactions (6.1)*]. Patients with an activated renin-angiotensin system, such as volume- and/or salt-depleted patients (e.g., those being treated with high doses of diuretics), are at greater risk. Correct volume or salt depletion prior to administration of [Entresto] or start at a lower dose. If hypotension occurs, consider dose adjustment of diuretics, concomitant antihypertensive drugs, and treatment of other causes of hypotension (e.g., hypovolemia). If hypotension persists despite such measures, reduce the dosage or temporarily discontinue [Entresto]. Permanent discontinuation of therapy is usually not required.
>
> **5.4 Impaired Renal Function**
> As a consequence of inhibiting the renin-angiotensin-aldosterone system (RAAS), decreases in renal function may be anticipated in susceptible individuals treated with [Entresto] [*see Adverse Reactions (6.1)*]. In patients whose renal function depends upon the activity of the renin-angiotensin-aldosterone system (e.g., patients with severe congestive heart failure), treatment with ACE inhibitors and angiotensin receptor antagonists has been associated with oliguria, progressive azotemia and, rarely, acute renal failure and death. Closely monitor serum creatinine, and down-titrate or interrupt [Entresto] in patients who develop a clinically significant decrease in renal function [*see Use in Specific Populations (8.7) and Clinical Pharmacology (12.3)*].
>
> As with all drugs that affect the RAAS, [Entresto] may increase blood urea and serum creatinine levels in patients with bilateral or unilateral renal artery stenosis. In patients with renal artery stenosis, monitor renal function.
>
> **5.5 Hyperkalemia**
> Through its actions on the RAAS, hyperkalemia may occur with [Entresto] [*see Adverse Reactions (6.1)*]. Monitor serum potassium periodically and treat appropriately, especially in patients with risk factors for hyperkalemia such as severe renal impairment, diabetes, hypoaldosteronism, or a high potassium diet. Dosage reduction or interruption of [Entresto] may be required [*see Dosage and Administration (2.6)*].[84]

[84] See Entresto Labeling, section 5.

2. Entresto's NDA 207620/S-018

In April 2020, Novartis submitted an efficacy supplement for Entresto's NDA 207620/S-018, Supplement 018. To support approval of this supplement, Novartis conducted a single-phase 3 clinical trial referred to as *PARAGON-HF* (PARAGON). PARAGON was a multicenter, randomized, double-blind trial comparing Entresto and valsartan in adult patients with symptomatic HF with LVEF greater than or equal to 45 percent, and structural heart disease (either left atrial enlargement or left ventricular hypertrophy).[85] The design of PARAGON employed various inclusion criteria, including that the study population consist of chronic HF patients who presented with a baseline measurement of LVEF greater than or equal to 45 percent within 6 months prior to screening (which includes patients with mildly reduced LVEF and patients with normal LVEF (i.e., both patients with and without evidence of left ventricular systolic dysfunction).[86]

Novartis referred to the study population of PARAGON as "HF patients with preserved ejection fraction" (or HFpEF), defining HFpEF based solely on the LVEF inclusion criteria employed in PARAGON (LVEF greater than or equal to 45 percent),[87] and it sought approval of an additional indication for Entresto: "to reduce worsening [HF] (total [HF] hospitalizations and urgent [HF] visits) in patients with chronic [HF] and preserved ejection fraction."[88] During the Agency's review of the PARAGON supplement, Novartis revised the study population of PARAGON from "patients with chronic [HF] and preserved ejection fraction" to "patients with chronic [HF] and preserved ejection fraction with LVEF below normal." Novartis accordingly proposed a revised indication: "to reduce worsening [HF] (total [HF] hospitalizations and urgent [HF] visits) in patients with chronic [HF] and preserved ejection fraction with LVEF below normal" (still defining HFpEF by the inclusion criteria LVEF greater than or equal to 45 percent).[89] Such revisions to PARAGON eliminated data on approximately half of the initial study population of PARAGON (i.e., the patients without evidence of left ventricular systolic dysfunction), leaving data on only HF patients with LVEF greater than or equal to 45 percent but below normal (i.e., the patients with evidence of left ventricular systolic dysfunction).[90] Additionally, Novartis

[85] See Entresto Labeling, section 14.

[86] See Entresto Supplement 018 Clinical Review(s) at 34 (PDF 65/176) (additionally noting that PARAGON employed various exclusion criteria, including that the study population not consist of chronic HF patients with LVEF less than 40 percent); see also at 13 (PDF 44/176).

[87] The American Society of Echocardiography (ASE) defines normal mean LVEF ± SD (2-SD range) as 62 ± 5 % (52-72) in males and 64 ± 5 % (54-74) in females as measured by echocardiography. Based on this definition, PARAGON-HF enrolled a heterogenous patient population that included patients both with mildly reduced/abnormal and normal LVEF. Clinical/Statistical Review for Entresto Supplement 018 Clinical Review(s) at 18 (PDF 49/176).

[88] See Entresto Supplement 018 Clinical Review(s) at 17 (PDF 48/176).

[89] See Entresto Supplement 018 Clinical Review(s) at 14 (PDF 45/176).

[90] See Entresto Supplement 018 Clinical Review(s) at 14 (PDF 45/176) ("Rationale for the revised definition of the intended population was as follows: (1) subgroup analysis finding of a RR of 0.78 in patients with LVEF ≤ 57% in

sought an additional indication based on a prespecified exploratory endpoint in PARAGON: "to reduce worsening [HF] (total [HF] hospitalizations and urgent [HF] visits)."[91]

The primary efficacy endpoint in PARAGON was the adjudicated composite of cardiovascular death and total (first and recurrent) hospitalization for HF. PARAGON-HF narrowly missed the predefined threshold for statistical significance for the primary composite endpoint, but prospectively planned exploratory analysis was conducted using an expanded composite endpoint combining the adjudicated primary efficacy endpoint with urgent HF visits (no overnight hospitalization was required).[92] These additional analyses evaluating certain other endpoints led to findings that suggested some treatment effect of Entresto in HF patients with LVEF greater than or equal to 45 percent.[93] Specifically, "subgroup analyses in PARAGON[] demonstrated a heterogeneity of treatment effect in two major subgroups, by sex and LVEF."[94] The Clinical Review explains the following regarding the benefit risk assessment of Entresto based on PARAGON:

> Analysis of treatment effect by LVEF as a continuous variable demonstrated that the following populations derive benefit with Entresto a) both males and females, albeit females benefit over a higher LVEF range, and b) **patients with mildly reduced (abnormal) LVEF / mild left ventricular systolic dysfunction**. Similar trends in treatment effect by LVEF were observed with candesartan in CHARM program and with spironolactone in RALES+TOPCAT. These observations suggest that patients with mildly reduced (abnormal) LVEF / mild left ventricular systolic dysfunction resemble patients with moderate to severely reduced/ abnormal LVEF, i.e.; patients with HFrEF in terms of treatment response to some of these therapies.
>
> * * * *
>
> The overall benefit risk assessment supports the approval of Entresto to reduce the risk of cardiovascular death and hospitalization for heart failure in patients with chronic heart failure, where the benefit appeared to be driven by patients with left ventricular ejection fraction below normal.[95]

PARAGON-HF, and (2) consideration of overlapping HF pathophysiology and hence response to Entresto between patients with mildly reduced/abnormal LVEF included in the subgroup of LVEF ≤ 57% and the adjacent patient population of HFrEF (LVEF < 40%) studied in PARADIGM-HF.").

[91] See Entresto Supplement 018 Clinical Review(s) at 14–15 (PDF 45–46/176).

[92] See Entresto Supplement 018 Clinical Review(s) at 14 and 17 (PDF 45 and 48/176).

[93] See Entresto Supplement 018 Clinical Review(s) at 14 (PDF 45/176).

[94] Entresto Supplement 018 Clinical Review(s) at 17 (PDF 48/176).

[95] See Entresto Supplement 018 Clinical Review(s) at 18 (PDF 49/176) (emphasis added); see also at 14 (PDF 45/176) ("Subgroup analyses demonstrated a heterogeneity of treatment effect by sex and LVEF suggesting that females and patients with LVEF ≤ 57%, derive a greater benefit with Entresto compared to males and patients with LVEF > 57%.").

On February 16, 2021, FDA approved Supplement 018, which resulted in revisions to Entresto's labeling, including substantive revisions to the INDICATIONS AND USAGE AND CLINICAL STUDIES sections and additional revisions throughout.[96] FDA added PARAGON data/information to section 14.1 and other sections of Entresto's labeling. FDA also revised Entresto's subsection 1.1 adult HF indication statement as illustrated below in Table 1 (additions shown in bold underline; deletions shown with strikethrough):

Table 1: Revisions to subsection 1.1 labeling for Entresto

Revisions to Entresto's Previously Approved Adult HF Indication Statement	**Entresto's Approved Adult HF Indication Statement in Supplement 018**
1.1 Adult Heart Failure Entresto is indicated to reduce the risk of cardiovascular death and hospitalization for heart failure in **[adult]**[97] patients with chronic heart failure ~~(NYHA Class II-IV) and reduced ejection fraction~~. ~~Entresto is usually administered in conjunction with other heart failure therapies, in place of an ACE inhibitor or other ARB.~~ **Benefits are most clearly evident in patients with left ventricular ejection fraction (LVEF) below normal.** **LVEF is a variable measure, so use clinical judgment in deciding whom to treat *[see Clinical Studies (14.1)]*.**	**1.1 Adult Heart Failure** Entresto is indicated to reduce the risk of cardiovascular death and hospitalization for heart failure in adult patients with chronic heart failure. Benefits are most clearly evident in patients with left ventricular ejection fraction (LVEF) below normal. LVEF is a variable measure, so use clinical judgment in deciding whom to treat *[see Clinical Studies (14.1)]*.

The publicly available Clinical Review for Supplement 018 explains that FDA "concluded that PARAGON[ ] did not support the first-ever claim in a fundamentally different form of [HF], but it did support an expansion of [Entresto's] prior claim."[98]

[96] See Entresto sNDA 207620/S-018 Approval Letter, available at https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2021/207620Orig1s018ltr.pdf ("This Prior Approval supplemental new drug application provides for updates to the United States Prescribing Information (USPI) and the Patient Package Insert (PPI) related to the PARAGON-HF trial, including substantive revisions to Indications and Usage and Clinical Studies; additional revisions were made throughout labeling.").

[97] See footnote 67, above, describing the approved indication for Entresto in pediatric patients.

[98] Entresto Supplement 018 Clinical Review(s) at 10 (PDF 41/176); see also at 85–86 (PDF 116–117/176).

The recommendation to approve Entresto with a revised indication statement with the approval of Supplement 018 was based on multiple considerations,[99] including input from a Cardiovascular and Renal Drugs Advisory Committee:

> The Advisory Committee voted 12 (yes), 1 (no), 0 (abstention) for an indication based on the totality of the evidence. Various proposals were advanced for the precise wording of the indication. Such proposals included prevention of heart failure hospitalizations in patients with an ejection fraction "less than the lower limit of normal," or a "mildly reduced ejection fraction." Several members favored using an LVEF range of 45-55%. Other members debated inclusion of LVEF < 57% based on the belief this would capture the higher threshold in women. One member raised concerns over imprecision in echocardiography. There was also substantial deliberation on use of the term "mildly reduced" ejection fraction because of subjectivity among treating physicians. The Advisory Committee thought that the evidence from PARAGON-HF supported the idea of a "continuum" of heart failure rather than distinct classifications of HFpEF and HFrEF. There was also support for a graded adjudication process.[100]

Novartis's Supplement 018 qualified for 3-year exclusivity based on PARAGON, which was denoted in FDA's Orange Book as M-82 (Labeling Revisions Related to Clinical Studies) and expired on February 16, 2024.

3. Patents for Entresto Listed in the Orange Book and Relevant to the Petition

Four patents that are relevant to the Petition are listed in the Orange Book for Entresto. Each is listed as a method of use patent:[101]

- U.S. Patent Nos. 9,517,226 (submitted for listing on March 16, 2021, and expiring August 22, 2033), 9,937,143 (submitted for listing on March 16, 2021, and expiring August 22, 2033), and 11,135,192 (submitted for listing on October 18, 2021, and expiring August 22, 2033), each listed with patent use code U-3084 (Treatment of Heart Failure With Preserved Ejection Fraction) (collectively, the HFpEF Patents).

- U.S. Patent No. 11,058,667 ('667 patent) (expires May 9, 2036), with patent use code of U-3170 (Treating Chronic Heart Failure With Reduced Ejection Fraction in Patients Not

[99] See Entresto Supplement 018 Clinical Review(s) at 10–11 (PDF 41–42/176) ("The recommendation to approve Entresto for the review team's proposed indication was based on the following: . . . 2) there is concordance of positive results between the Intention-to-Treat (ITT) subjects in the antecedent PARADIGM-HF trial that met the success criteria, and the subgroup of subjects with reduced LVEF in the PARAGON-HF trial; . . . and 6) there was concordance among [the Cardiovascular and Renal Drugs Advisory Committee], [the Division of Cardiology and Nephrology] and [the Medical Policy and Program Review Committee] that data from PARAGON-HF supported the expansion of indicated population to include patients with mildly reduced LVEF.").

[100] Entresto Supplement 018 Clinical Review(s) at 12 (PDF 43/176). See also at 85–86 (PDF 116–117/176).

[101] See Orange Book Listing for Entresto, https://www.accessdata.fda.gov/scripts/cder/ob/patent_info.cfm?Product_No=001&Appl_No=207620&Appl_type=N.

Taking an ACE Inhibitor or an ARB or Previously Taking Low Doses of These Agents, by Titrating Up From Half the Usually Recommended Starting Dose)."

III. DISCUSSION

You contend that the 3-year exclusivity related to the PARAGON study protects the use of Entresto in "an expanded population of all patients with chronic heart failure – including patients with HFpEF."[102] You further contend that all of the February 2021 revisions made to Entresto's labeling, including those made to its indication, are within the scope of Entresto's exclusivity.[103] At the same time, you acknowledge a nonprotected condition of use for Entresto[104] but argue that Entresto's current HF indication makes it impossible for generic sacubitril and valsartan products to be labeled for only that nonprotected use.[105] You argue that omitting certain language from Entresto's current indication statement would result in an overly broad indication for generic sacubitril and valsartan products, and that otherwise revising the indication (e.g., by adding language to carve out the protected conditions of use) is impermissible under certain statutory and regulatory provisions concerning the labeling of drug products proposed under an ANDA.[106]

You make similar arguments regarding the HFpEF Patents, alleging that the method of use claimed by these patents cover the February 2021 revisions to Entresto's labeling describing the results of the PARAGON study and "the expanded indication statement directed to patients with HFpEF."[107] You argue that a section viii statement to the HFpEF Patents is impermissible, alleging that Entresto's current HF indication makes it impossible for generic sacubitril and valsartan product applicants to carve out the purported use protected by these patents.[108]

Thus, you argue that both the 3-year exclusivity related to the PARAGON study and the HFpEF Patents prohibit FDA from approving a generic sacubitril and valsartan product referencing Entresto for any use, including any nonprotected use, "until expiration of the exclusivity in February 2024 – and even then, only if the ANDA applicants submit a paragraph IV certification to each of the HFpEF Patents."[109] Notably, you do not contend that any permissible carve out of protected information would render a generic sacubitril and valsartan product any less safe or effective than Entresto for the remaining nonprotected conditions of use.

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[102] Petition at 13.

[103] See Petition at 2, 13–16.

[104] See Petition at 19 ("In the case of [Entresto], the use in heart failure patients with reduced ejection fraction is not protected by the HFpEF Patents and the 3-year exclusivity.").

[105] See, e.g., Petition at 19, 23.

[106] See Petition at 16–22.

[107] See Petition at 16.

[108] See, e.g., Petition at 4.

[109] See Petition at 23.

Additionally, you argue that ANDA applicants referencing Entresto as the RLD cannot omit the modified dosing regimen reflected in subsection 2.6 of Entresto's labeling by submitting a section viii statement to the '667 patent.[110] You assert that the '667 patent's use code in the Orange Book covers the modified dosing regimen described in subsection 2.6, and that ANDA applicants seeking to submit a section viii statement to the '667 patent would need to omit the modified dosing information "for adult HFrEF patients and for pediatric HFrEF patients weighing more than 50 kg."[111] You assert that omitting such information from generic sacubitril and valsartan product labeling would likely increase the rates of clinically significant adverse events in certain patients and could also result in decreased efficacy.[112] Thus, you contend that the modified dosing information in subsection 2.6 cannot be carved out of generic sacubitril and valsartan product labeling because doing so would render the generic product less safe and effective than Entresto for the remaining nonprotected conditions of use.[113]

We address your contentions below.

A. 3-Year Exclusivity Request Is Moot

You assert in the Petition that the scope of the 3-year exclusivity recognized for Entresto Supplement 018 includes all of the revisions to Entresto's labeling approved on February 16, 2021.[114] Thus, you contend that FDA is "prohibited from approving an ANDA until February 16, 2024 for the conditions of approval arising from the 2021 supplement."[115] This request is moot because, regardless of the scope of the exclusivity recognized for Entresto Supplement 018, the exclusivity expired on February 16, 2024.

Accordingly, the Petition's first request is dismissed as moot.

B. ANDA Applicants Can File a Section viii Statement and Propose Labeling That Does Not Seek Approval for the Use Protected by the HFpEF Patents

Novartis submitted two of the HFpEF Patents in March 2021 and a third in October 2021 for listing in the Orange Book. Consistent with the Agency's ministerial role in the listing of patents, and based on Novartis's description of what it purports is a specific approved method of use of Entresto claimed by the patents, FDA listed the HFpEF Patents in the Orange Book with the use code U-3084 (Treatment of Heart Failure With Preserved Ejection Fraction). As described above, while FDA does not independently evaluate the information provided in the use code in relation to the patent, we nevertheless regularly evaluate what portions of labeling

[110] See Petition at 4, 23–30.

[111] See Petition at 24.

[112] See, e.g., Petition at 24–26.

[113] See, e.g., Petition at 26.

[114] See, e.g., Petition at 13.

[115] See, e.g., Petition at 13.

appropriately correspond to the use code provided and whether ANDAs may be approvable with labeling that carves out protected information that corresponds to the use code provided. Such determinations fall squarely within the ambit of FDA's scientific expertise.[116]

When a patent is listed in the Orange Book for a method of use, an ANDA applicant seeking to omit that approved method of use covered by the listed patent may submit a *section viii statement* acknowledging that a method of use patent has been listed for the drug but stating that the patent at issue does not claim a use for which the applicant seeks approval. Specifically, section 505(j)(2)(A)(viii) of the FD&C Act provides that:

> If with respect to the listed drug referred to in [section 505(j)(2)(A)(i)] information was filed under subsection (b) or (c) for a method of use patent which does not claim a use for which the applicant is seeking approval under this subsection, [the ANDA must contain] a statement that the method of use patent does not claim such a use.

Submission of a section viii statement requires the ANDA applicant to omit from its labeling information pertaining to the protected use. If an ANDA applicant files a section viii statement (and proposes labeling that does not seek approval for the protected use), the patent claiming the protected method of use will not serve as a barrier to ANDA approval. In determining the propriety of a labeling carve out under this section, consistent with its ministerial role, FDA compares the patent information provided by the NDA applicant with the drug's approved labeling and determines whether a drug with the patented use carved out remains safe and effective for the remaining nonprotected conditions of use.[117]

You assert that the "new use approved in February 2021 for patients with chronic heart failure, including patients with preserved ejection fraction, is protected by . . . the HFpEF Patents listed in the Orange Book."[118] You also assert that the "labeling describing the clinical study results from PARAGON[] and the expanded indication statement directed to patients with HFpEF are covered by the method of use claimed by the HFpEF Patents, as described in the published [u]se [c]ode."[119] You argue that "there is no permissible way for ANDA applicants to draft an indication statement for use in patients with reduced ejection fraction by deleting words or making *de minimis* changes to the existing indication statement."[120] We reject your arguments.

In accordance with our statutory and regulatory authority, we have determined that in this instance, an ANDA may propose labeling for a generic sacubitril and valsartan product that does not seek approval for the purported use protected by the HFpEF Patents. There are three reasons underlying this determination.

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[116] See, e.g., Letter from J. Woo, Acting Director of FDA's ORO/OGD/CDER, to Dexmedetomidine Hydrochloride Injection NDA Holder/ANDA Applicant, Docket No. FDA-2014-N-0087 at 8 (Aug. 18, 2014).

[117] Under the FD&C Act, an ANDA applicant must submit either a patent certification or a section viii statement for each listed patent for the RLD. Section 505(j)(2)(A)(vii) through (viii) of the FD&C Act.

[118] Petition at 22.

[119] Petition at 16.

[120] Petition at 23.

First, we disagree that Entresto's approved indication statement and labeling describing the clinical study results from PARAGON reflect an approved use of Entresto in *all* chronic HF patients. As explained below in section III.B.1, PARAGON did not demonstrate a benefit of Entresto in *all* HF patients. PARAGON also did not demonstrate a benefit of Entresto in patients with a "fundamentally different form of heart failure."[121] However, PARAGON did support the expansion of Entresto's prior claim to include patients with a broader range of LVEF, including patients in the normal range of LVEF.

Second, while we reject your position that HFpEF should be defined merely as LVEF above what Novartis has referred to as an "arbitrary LVEF cut-point," the Agency acknowledges that PARAGON allowed for the expansion of Entresto's prior claim such that the updated indication statement includes patients who could be categorized within prevailing definitions of HFrEF or HFpEF.

Third, we reject your assertion that we must refrain from approving any ANDA referencing NDA 207620 that contains a section viii statement to the HFpEF Patents because there is no way to "draft an indication statement for a proposed ANDA product by deleting the use protected by the HFpEF Patents from the current Entresto indication statement."[122]

1. PARAGON Did Not Demonstrate a Benefit of Entresto in 'all' HF Patients

Contrary to your claims in the Petition, the PARAGON study did not support the use of Entresto in "all" patients with chronic HF.[123] However, as explained further below, the Agency has concluded that the PARAGON study conducted by Novartis to support the approval of Supplement 018 demonstrated that the fixed combination of sacubitril, a neprilysin inhibitor, and valsartan, an ARB (i.e., RAS inhibitor) could be safe and effective for some adult chronic HF patients whose LVEF was greater than or equal to 45 percent at the time of study initiation. The PARAGON study confirmed that Entresto would benefit the adult HF population whose reduced LVEF at initiation provided evidence of impaired contraction (like the adult HF patients studied previously in PARADIGM, whose LVEFs were less than or equal to 40 percent at the time of study initiation) while demonstrating that Entresto could benefit patients with a broader range of LVEF below normal. The publicly available Clinical Review for Supplement 018 explicitly states that "PARAGON[] did not support the first-ever claim in a fundamentally different form of heart failure, **but it did support an expansion of [Entresto's] prior claim.**"[124]

[121] See Entresto Supplement 018 Clinical Review(s) at 10 (PDF 41/176).

[122] See Petition at 4.

[123] See Petition at 13.

[124] Entresto Supplement 018 Clinical Review(s) at 10 (PDF 41/176) (emphasis added).

a. HF and Entresto before PARAGON

Prior to PARAGON, it was known that Entresto was safe and effective for adult patients with chronic HF in the setting of impaired contraction (i.e., for some HF patients with below normal LVEF at baseline).[125] FDA initially approved Entresto for use in adults "to reduce the risk of cardiovascular death and hospitalization for heart failure in patients with chronic heart failure (NYHA class II–IV) and reduced ejection fraction," as reflected in the then-approved product labeling that also described and included data from the only clinical efficacy study supporting such use at the time, PARADIGM.[126] PARADIGM was a multinational, randomized, double-blind trial comparing Entresto and enalapril in adult patients with symptomatic chronic HF (NYHA class II–IV) and systolic dysfunction.

Prior to PARAGON, clinicians understood that a drug approved to treat an adult patient population with chronic HF and reduced ejection fraction, like Entresto, would benefit some patients with both evidence of HF and evidence of an underlying mechanism of systolic dysfunction, or in plain terms, impaired contraction. Clinicians understood that the evidence supporting the setting of impaired contraction likely originated from a study on HF patients with a baseline moderate to severely reduced/abnormal LVEF measurement (likely LVEF less than or equal to 40 percent, but sometimes less than or equal to 35 percent or less than or equal to 45 percent, verifiable by reference to the clinical data). This was indeed the case for Entresto where, similar to previous studies on other HF treatments known to have benefits in HF in the setting of impaired contraction, PARADIGM was designed to employ an LVEF cutoff of less than or equal to 40 percent as one of various inclusion criteria of the study. As noted above, a study employing such a cutoff was not designed based on a comprehensive inclusion of all patients whose below normal LVEF at baseline could reasonably be considered evidence of impaired contraction (i.e., it leaves out HF patients with baseline LVEF greater than 40 percent but below normal). Rather, studies like PARADIGM were designed to employ what Novartis itself has described as an "arbitrary LVEF cut-point,"[127] which would have been considered by clinicians incorporating clinical judgment to make diagnosis and treatment decisions in a clinical setting. In other words, while the phrase "HF and reduced ejection fraction" may be defined by some as HF with LVEF less than or equal to 40 percent, the underlying meaning of the phrase reflects the clinical setting of impaired contraction supported by LVEF data below normal.

As explained above, currently (and prior to PARAGON) impaired contraction is recognized as one of four distinct phenotypes (or mechanisms) of HF because the pathophysiology of such mechanism is well supported by scientific evidence. LVEF has long been known as one of many measures of cardiac performance used by health care practitioners in clinical practice to assist in the diagnosis and treatment of HF. As explained above, it is well understood that low LVEF is one measure of the effectiveness of the heart to push blood forward in the circulation, and that a

[125] See background discussion on HF above in section II.A.

[126] We note that public versions of the Reviews for Entresto, which provide additional context regarding Entresto and PARADIGM, have been available on FDA's website since shortly after Entresto's initial approval in 2015.

[127] See December 15, 2020, Novartis Presentation on Sacubitril/Valsartan (Entresto) at FDA's Cardiovascular and Renal Drugs Advisory Committee Meeting at 20, available at https://web.archive.org/web/20210305025644/https://www.fda.gov/media/144448/download.

below normal LVEF provided strong evidence that the heart's ability to contract was impaired. Before PARAGON, the variability associated with LVEF measurements was well known, because they are operator-dependent, require adequate acoustic windows, and rely on geometrical assumptions, making it difficult to distinguish a patient's LVEF reliably within better than 5 percent. This is in addition to known uncertainties about applying findings from population-level LVEF when considering use of a HF treatment in an individual patient and a lack of modeling of the true dependence of LVEF on time. HF tends to worsen, and LVEF generally declines over time. Over the short term, there can be true improvements and noise in the LVEF measurements, meaning that a patient presenting one day with severely reduced/abnormal LVEF may later present with mildly reduced/abnormal LVEF or with normal LVEF. In light of these considerations, clinicians have long understood the importance of incorporating clinical judgment in the context of baseline LVEF findings and would not have strictly relied on a baseline LVEF measurement alone as the sole basis for diagnosis and treatment decisions. Moreover, and contrary to the implications of the assertions in your Petition, Entresto's labeling prior to PARAGON did not restrict the use of Entresto strictly to patients with LVEF less than or equal to 40 percent, neither for starting nor for continuing treatment of HF patients whose LVEFs rose above the PARADIGM inclusion criterion.[128] We disagree with the flawed suggestion that clinicians would have interpreted Entresto's previous indication statement to implicitly incorporate an "arbitrary LVEF cut-point" as a strict diagnostic criterion into the approved use reflected by Entresto's initial approval and in its prior labeling. As explained above, clinicians would have understood that the study supporting the indication likely employed an LVEF cutoff of less than or equal to 40 percent. The clinical data is included in Entresto's labeling to not only confirm the design of PARADIGM but also to consider any statistical analysis of the study results included in the labeling.

Since its initial approval, Entresto's labeling has described PARADIGM as a study on "adult patients with symptomatic chronic [HF] . . . and systolic dysfunction ([LVEF] ≤ 40%),"[129] expressly conveying both the setting in which the drug was studied (systolic dysfunction, i.e., impaired contraction) and the range of baseline LVEF measurements over which the drug had been studied supporting the recognition of such setting. In our view, because clinicians understood the variability associated with LVEF measurements, and that PARADIGM was not designed to include a comprehensive inclusion of all patients with impaired contraction, clinicians would have considered the PARADIGM data provided in Entresto's labeling to further inform treatment and diagnosis decisions. For example, Figure 4 in Entresto's original labeling was a forest plot of only PARADIGM data, showing the treatment effect in PARADIGM by quartile of baseline LVEF. This data would have suggested that there was no sharp decline in effectiveness in the upper quartile (the upper range of the LVEF of its inclusion criterion). Given the considerations discussed above that are specific to the treatment of the HF syndrome, we believe that clinicians would have reasonably incorporated into their clinical judgment an

[128] See Petition at 3 (characterizing the approval of Supplement 018 as "reflect[ing] the agency's decision to no longer use LVEF as a strict diagnostic criterion to determine which patients may benefit from [Entresto]").

[129] See Entresto Labeling, subsection 14.1.

inference from PARADIGM that the effectiveness of Entresto would extend somewhat above baseline LVEF of 40 percent, which is wholly consistent with Entresto's original indication.[130]

Your suggestion that Entresto's original indication statement would have been understood as restricting the use of Entresto strictly to patients with LVEF less than or equal to 40 percent because it included the phrase "and reduced ejection fraction" ignores a multitude of considerations relevant to the treatment of HF in clinical practice discussed throughout this response and known prior to PARAGON, including: the recognized mechanisms of HF (which are reasonably based on pathophysiology); the type of data that provides evidence of such mechanisms; the controversial nature of the still evolving nomenclature being used by some to classify HF, particularly in the settings of clinical trials and published guidelines; certain shortcomings with and variability in LVEF measurements; data from PARADIGM and other trials in HF; and the well-understood importance of incorporating clinical judgment in the context of the LVEF findings rather than using a specific LVEF value alone as the basis for treatment.

Accordingly, prior to the approval of Supplement 018, it was known that PARADIGM enrolled patients with LVEF less than or equal to 40 percent and established the efficacy of Entresto in this population with HF and *reduced* (or *below normal*) LVEF, which in clinical practice was and is widely understood as representing HF patients with impaired contraction (i.e., systolic dysfunction).

b. HF and Entresto after PARAGON

PARAGON illustrated that impaired contraction does not sharply end at LVEF of 40 percent for the fixed combination of a neprilysin inhibitor plus an angiotensin receptor blocker.[131] In contrast to PARADIGM, PARAGON was the first clinical trial to provide direct evidence demonstrating a benefit of Entresto in some adult HF patients with an LVEF greater than or equal to 45 percent at the start of treatment. PARAGON was designed to study Entresto in adult patients with symptomatic HF and certain structural heart disease (either left atrial enlargement or left ventricular hypertrophy) and employed a baseline LVEF measurement of greater than or equal to 45 percent as one of various inclusion criteria of the study.[132]

Whereas PARADIGM supported a claim in what has been referred to as HF with reduced ejection fraction or HFrEF, Novartis purported to conduct PARAGON to support a claim for HF with preserved ejection fraction or HFpEF. As explained above, HFpEF as a clinical entity has historically been considered in practice to represent a fundamentally different form of HF than

[130] An illustrative example would be to consider a patient presenting with evidence of HF and a baseline LVEF measurement of 41 percent.

[131] We note that PARAGON joins earlier studies, TOPCAT (spironolactone, a mineralocorticoid receptor antagonist) and CHARM (candesartan, an angiotensin receptor blocker), with similar but unlabeled findings that their benefits do not cease at an LVEF of 40 percent.

[132] See Entresto Labeling, subsection 14.1.

that of HFrEF.[133] However, in the context of PARAGON, Novartis simply defined HFpEF based on the LVEF exclusion criterion employed in the study, "HF with LVEF ≥ 45%."[134] Novartis's stated rationale for employing an LVEF cutoff of greater than or equal to 45 percent was "to exclude patients who had borderline [HF] with reduced ejection fraction (HFrEF),"[135] again relying merely on the "arbitrary LVEF cut-point" employed in PARADIGM to purportedly distinguish and define a patient population as one with a different form of HF than what was studied in PARADIGM.[136] Notably, employing an LVEF cutoff of greater than or equal to 45 percent resulted in a heterogeneous patient population enrolled in the study, which meant that PARAGON enrolled HF patients with mildly reduced/abnormal LVEF and HF patients with normal LVEF (i.e., together, patients with and without evidence of impaired contraction).[137] Novartis initially defined the intent-to-treat population as "patients with chronic [HF] and preserved ejection fraction," which referred to the entire population of PARAGON based on Novartis's definition for HFpEF.[138] During the review cycle, however, Novartis revised the intended population to "patients with chronic [HF] and preserved ejection fraction with LVEF below normal," which referred to approximately half of the study population of PARAGON (based on Novartis's definition of HFpEF) and limited the study population to only the HF patients whose below normal LVEF at the start of the trial provided evidence of impaired contraction.[139]

The results of PARAGON did not meet the prespecified criteria for success, but the Agency agreed to review the data from PARAGON because a marginally significant result ($p = 0.06$) established benefit of Entresto in HF and a consistent rate ratio[140] was demonstrated by exploratory and sensitivity analyses.[141] The Clinical Review for Supplement 018 explains that "[a]nalysis of treatment effect by LVEF as a continuous variable demonstrated that the following populations derive benefit with Entresto a) both males and females, albeit females benefit over a

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[133] See, e.g., the draft guidance for industry *Treatment of Heart Failure: Endpoints for Drug Development* (June 2019), at 1 (referring to "[HF] with reduced ejection fraction (HFrEF)" and "[HF] with preserved ejection fraction (HfpEF)" as separate and distinct clinical entities). When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

[134] See Entresto Supplement 018 Clinical Review(s) at 14 (PDF 45/176); see also at 11 (PDF 42/176) ("The definition of HFpEF varies across clinical trials (i.e., ≥ 40% or ≥ 45% or ≥ 50%).").

[135] Entresto Supplement 018 Clinical Review(s) at 34 (PDF 65/176).

[136] See December 15, 2020, Novartis Presentation on Sacubitril/Valsartan (Entresto) at FDA's Cardiovascular and Renal Drugs Advisory Committee Meeting ("HFpEF–originally defined as everything else left over i.e., defined by not having a 'reduced' LVEF (<40%).").

[137] See Entresto Supplement 018 Clinical Review(s) at 14 (PDF 45/176).

[138] See Entresto Supplement 018 Clinical Review(s) at 14 (PDF 45/176).

[139] See Entresto Supplement 018 Clinical Review(s) at 14 (PDF 45/176)

[140] Generally, a *rate ratio* is the ratio of incidence rates in the treated and untreated groups of a study.

[141] See Entresto Supplement 018 Clinical Review(s) at 10 (PDF 41/176).

higher LVEF range, and b) **patients with mildly reduced/abnormal LVEF**."[142] The Agency concluded that, while some of the PARAGON data did support an expansion of Entresto's previous adult HF claim, PARAGON "did not support the first-ever claim in a fundamentally different form of [HF]."[143] The Agency also concluded that the benefit observed in PARAGON was not apparent in the population with normal LVEF at baseline.[144] Specifically, the publicly available Clinical Review for Entresto Supplement 018 explains the Agency's position on the results of PARAGON:

> The review team concluded that PARAGON-HF did not support the first-ever claim in a fundamentally different form of heart failure, **but it did support an expansion of [Entresto's] prior claim.**
>
> * * *
>
> In the PARAGON-HF trial, 46% of the [intend-to-treat] ITT population had an LVEF < 55%. Subgroup analyses of the PARAGON-HF trial for the adjudicated primary efficacy endpoint showed that subjects with an LVEF below the median (LVEF 57%) appeared to derive benefit (rate ratio 0.78, 95% CI 0.64-0.95) more than subjects with an LVEF above the median (rate ratio 1.00, 95% CI 0.81-1.23). The apparent benefit in subjects with reduced LVEF was consistent with the evidence from the PARADIGM-HF trial. **The benefit was not apparent in the population with normal LVEF as defined by the ASE**. The review team considered PARAGON-HF to provide supportive evidence of efficacy in the heart failure population with reduced LVEF as already demonstrated in the PARADIGM-HF trial, **but with an expanded range of LVEF below normal**.[145]

Thus, while the originally approved indication statement was more explicit about the population in whom the PARADIGM study had demonstrated effectiveness — "patients with chronic heart failure (NYHA Class II–IV) and reduced ejection fraction" — it did not restrict use to below a specific cutoff LVEF, even as the indication limited use to those with "reduced ejection fraction."[146] Upon approval of Supplement 018, the indication statement became less specific and included uncertainty about the range of LVEF over which Entresto was likely to be effective.

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[142] See, e.g., Entresto Supplement 018 Clinical Review(s) at 14 (PDF 45/176) (emphasis added). (See also, id., "Similar trends in treatment effect by LVEF were observed with candesartan in CHARM program and with spironolactone in RALES+TOPCAT. These observations indicate that patients with mildly reduced LVEF or mild left ventricular systolic dysfunction resemble patients with moderate to severely reduced LVEF in terms of therapeutic response to these therapies.")

[143] See Entresto Supplement 018 Clinical Review(s) at 10–11 (PDF 41–42/176); see also Entresto Supplement 018 Other Review(s) at PDF 165/176 (emphasis added) ("The review team recommended approval of the application as an expansion of its prior claim and not as a 'first-ever claim in a fundamentally different form of heart failure' (HFpEF).")

[144] See Entresto Supplement 018 Clinical Review(s) at 11 (PDF 42/176) (noting "normal" LVEF as defined by ASE).

[145] See Entresto Supplement 018 Clinical Review(s) at 11 (PDF 42/176) (emphasis added).

[146] See Original Entresto Labeling (Rev. 7/2015), subsection 1.1.

The current labeling relies more upon the clinical trials section and physician judgment to determine limits of use.[147]

Although not immediately clear from the indication statement in the revised section 1 of the prescribing information, the revised labeling approved in Supplement 018 broadened the indication, in part by dropping *reduced*, but mostly by informing use with a description of the PARAGON results, which supported use across a broader range of LVEF than one could reasonably have inferred from PARADIGM alone. At the same time, the revised indication statement suggests that it may not be effective at the upper range of LVEF. The revised labeling does not assure effectiveness regardless of LVEF. Because the language casts doubt on the efficacy of Entresto across the full range of LVEF, the indication does not include *all* adult patients with chronic HF.

2. Entresto Supplement 018 Expanded the Indicated Population

While we reject your position that HFpEF is necessarily defined as LVEF above an "arbitrary LVEF cut-point," the Agency acknowledges that PARAGON allowed for the expansion of Entresto's prior claim such that the updated indication statement includes patients who could be categorized within prevailing definitions of HFrEF or HFpEF. Furthermore, the Agency concludes that, if HFpEF is taken to mean patients with HF and LVEF above some value, the information added to the labeling with the approval of Supplement 018 describes the "HFpEF subset" of the approved patient population.

a. Baseline LVEF measurement alone is insufficient to distinguish HFpEF

As you acknowledge, neither preserved ejection fraction nor HFpEF are used to describe any of Entresto's approved conditions of use and do not appear anywhere in Entresto's approved labeling, including in the indication statement. This was not an accident, especially given the still evolving and controversial nature of the definition of HFpEF, as well as the lack of well-defined, clinically useful parameters supported by data demarcating a clinical entity referred to as HFpEF from other recognized forms of HF. As discussed, HF syndrome simply means that the heart is not meeting the metabolic needs of the body. Cardiologists recognize a phenotype in which the heart contracts poorly and is often dilated. Low LVEF is one measure of the effectiveness of the heart to push blood forward in the circulation. Cardiologists also recognize a phenotype, usually characterized by a small, stiff heart, where the main problem appears to be filling the heart with blood to be pumped out during systole. Not all patients displaying either phenotype probably have the same underlying disease, and patients can have elements of both phenotypes.

Researchers dichotomize in deciding whom to enroll in a study and in deciding whom to treat, but nature does not. HF with reduced ejection fraction, while traditionally understood as representing HF patients with impaired contraction as evidenced by a below normal LVEF, has come to be characterized by the LVEF cutoffs employed as inclusion/exclusion criteria in

[147] Gandotra C, et al., Heart Failure Population With Therapeutic Response to Sacubitril/Valsartan, Spironolactone and Candesartan: FDA Perspective, Ther Innov Regul Sci, 2021, 56(1):4–7.

clinical studies (typically, LVEF of less than or equal to 40 percent or 45 percent). This cutoff was driven by various factors, including interest in having a high enough rate of mortality and hospitalization to make the studies feasible, but it was not based on comprehensive inclusion of all patients with impaired contraction. Studies typically used cutoffs of 40 percent or 45 percent, because they had similar interests in enrichment and because this cutoff got incorporated into resulting published guidelines as "HF with reduced ejection fraction" or "HFrEF." LVEF above such HFrEF cutoffs eventually became associated with the term *HF with preserved ejection fraction* or HFpEF, or, perhaps, also arbitrarily, *mid-range* in some clinical trials and resulting published guidelines, despite the original intent of the term HFpEF being to differentiate HF in which the mechanism for contraction was impaired from HF more likely to represent impaired relaxation. This criterion based solely on LVEF has the virtue of being easy to implement in practice, but it does not correspond to any useful clinical definition, which might reasonably be based on pathophysiology or response to treatment. The Agency, therefore, was avoiding reference in Entresto's labeling to "preserved" or "HFpEF" because it rejects the notion that a baseline LVEF measurement alone is sufficient to distinguish HFpEF as a fundamentally different form of HF, and because PARAGON data did not otherwise support the first-ever claim in a fundamentally different form of HF.

Accordingly, whether Entresto has a claim in the treatment of HF with preserved ejection fraction is a matter of semantics versus science. At present, a definition of HFpEF based solely on LVEF does not correspond to any useful clinical definition of disease state, particularly given that traditional notions associate the term HFpEF with the mechanism of HF representing impaired relaxation. There is little to no evidence that Entresto is safe and effective in treating such mechanism of HF. However, as noted above, operational definitions of HFpEF based on LVEF ranges have been included in published guidelines.[148] The PARAGON data demonstrated that Entresto is safe and effective in treating impaired contraction in certain patients who fall within the LVEF range that some published guidelines operationally define as HFpEF.

b. Entresto Supplement 018 expanded the indicated population to a subset of HFpEF patients

While Supplement 018 did not support the use of Entresto in "a fundamentally different form of heart failure," it did support an expansion of Entresto's prior claim such that the updated indication statement includes patients who could be categorized within prevailing definitions of HFrEF or HFpEF.

PARAGON demonstrated the effectiveness of Entresto in patients who met the study's inclusion criterion of LVEF greater than or equal to 45 percent. This LVEF cutoff was explicitly how the study designers defined HFpEF.[149] Patients with an LVEF greater than or equal to 45 percent were excluded from the PARADIGM trial, which only included patients with an LVEF less than or equal to 40 percent, and, therefore, were not explicitly included in the labeled indication upon Entresto's initial approval.

[148] See section II.A.1 above.

[149] Solomon SD, et al., Angiotensin Receptor Neprilysin Inhibition in Heart Failure With Preserved Ejection Fraction: Rationale and Design of the PARAGON-HF Trial, JACC Heart Fail, 2017, 5(7):471–482.

As described above, based upon standard, currently accepted definitions, HFpEF can include patients with normal LVEF, which is defined as LVEF above 50 percent. PARAGON included patients meeting this definition of HFpEF. The updated indication statement following the approval of Supplement 018 therefore includes patients who could be categorized within prevailing definitions of HFrEF or HFpEF, with information in section 14 that provides greater clarity on which patients see the most benefit.

3. ANDAs Containing Section viii Statements Can Omit the Expanded Population

Novartis submitted the three HFpEF Patents in 2021 for listing in the Orange Book. Consistent with the Agency's ministerial role in listing patent information, FDA listed the HFpEF Patents in the Orange Book with the use code U-3084 (Treatment of Heart Failure With Preserved Ejection Fraction).

As noted above, Entresto's labeled indication was expanded upon approval of Supplement 018 to include patients who could be categorized within prevailing definitions of HFpEF. Thus, the Supplement 018 labeling changes constitute approval in a subset of HFpEF patients. Therefore, we conclude that ANDA applicants can omit this information to propose labeling for a generic sacubitril and valsartan product that does not seek approval for the purported use protected by the HFpEF Patents.

A generic sacubitril and valsartan product bearing such labeling remains safe and effective for the nonprotected conditions of use. Furthermore, we reject your assertions that FDA cannot approve such generic sacubitril and valsartan product labeling because the Agency is precluded from "adding language or making more than *de minimis* changes to the existing indication statement"[150] or that doing so would necessitate "rely[ing] on discontinued labeling."[151]

a. ANDAs containing section viii statements can omit the information protected by the HFpEF Patents

Submission of a section viii statement requires the ANDA applicant to omit from its labeling information pertaining to the protected use. An applicant submitting an ANDA for a generic sacubitril and valsartan product can submit a section viii statement omitting the uses protected by the HFpEF Patents by proposing labeling that does not seek approval for use in the subset of HFpEF patients for which Entresto is approved. An illustrative example of such labeling is provided below (additions shown in bold underline; deletions shown with strikethrough):

1. INDICATIONS AND USAGE
1.1 Adult Heart Failure
Entresto is indicated to reduce the risk of cardiovascular death and hospitalization for heart failure in adult patients with chronic heart failure~~.~~ **and reduced ejection fraction.** ~~Benefits~~

[150] See Petition at 23.

[151] See Petition at 20.

~~are most clearly evident in patients with left ventricular ejection fraction (LVEF) below normal.~~

~~LVEF~~**Left ventricular ejection fraction (LVEF)** is a variable measure, so use clinical judgment in deciding whom to treat *[see Clinical Studies (14.1)]*.

The revised first paragraph of the indication statement does not disclose information regarding use of Entresto in any patient population that could be categorized as having preserved ejection fraction based on prevailing definitions.

Additionally, the retention of the second paragraph, which states that "LVEF is a variable measure, so use clinical judgment in deciding whom to treat," is appropriate because this statement does not disclose any information regarding use in any patient population that could be categorized as having preserved ejection fraction based on prevailing definitions.

Given that the PARAGON data submitted in Supplement 018 allowed for the expansion of Entresto's prior indication such that the updated indication statement includes patients who could be categorized within prevailing definitions of HFpEF, these data could be omitted from subsection 6.1 (Clinical Trials), subsection 8.5 (Geriatric Use), subsection 12.2 (Pharmacodynamics), and section 14 (Clinical Studies) of the labeling.[152]

Therefore, an ANDA applicant may submit a section viii statement and the proposed labeling illustrated above, along with other related changes in the prescribing information, without impermissibly disclosing any information protected by the HFpEF Patents.

b. Omission of information protected by the HFpEF Patents would not render generic sacubitril and valsartan less safe or effective for the remaining conditions of use

Omission of the information protected by the HFpEF Patents from ANDA labeling for a generic sacubitril and valsartan product would not render such products less safe or effective for the remaining conditions of use. While the Agency acknowledges the decision in the approval of Supplement 018 to use less specific terminology and to expand Entresto's indication statement based on the patient population in which it has been studied beyond an LVEF of 40 percent in PARAGON, this does not make it any less accurate or less safe to describe benefits in patients with LVEF less than or equal to 40 percent or to use the term *reduced ejection fraction* in omitting the use protected by the HFpEF Patents.

Regardless of the specific labeling changes approved in Supplement 018, a sacubitril and valsartan product remains safe and effective for use in patients with reduced ejection fraction. Indeed, in the initial submission of Supplement 018, Novartis proposed retaining this indication language and adding a second indication "to reduce worsening heart failure … in patients with

[152] Entresto Labeling (April 12, 2024), available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/207620s025,218591s000lbl.pdf.

chronic heart failure and preserved ejection fraction."[153] The Agency did not adopt this proposal for Entresto to bear two indications for treatment of HF because, as described above, the terms HFrEF and HFpEF have definitions in common usage that do not necessarily correspond to established disease in the HF setting. Therefore, the changes to the indication statement approved in Supplement 018 do not suggest that a sacubitril and valsartan product is not safe or effective for the treatment of chronic HF in patients with reduced ejection fraction.

c. Approval of ANDAs omitting information protected by the HFpEF Patents does not violate the *same labeling* requirement

You assert that "there is no permissible way for ANDA applicants to draft an indication statement for use in patients with reduced ejection fraction by deleting words or making *de minimis* changes to the existing indication statement."[154] We disagree. We have determined that, in this case, the modifications in the illustrative labeling to remove references to patent-protected information are consistent with the statute and applicable regulations, including 21 CFR 314.94(a)(8)(iv) and can adequately ensure that the carved-out labeling is not less safe or effective for the remaining conditions of use without disclosing the protected information.

d. The Agency can approve ANDA labeling that adds language

You assert further that "[a]dding words to the labeling of a proposed sacubitril and valsartan ANDA product's indication statement would impermissibly exceed the type of minor stylistic edits previously described by the [A]gency."[155] You rely on FDA's history of "selective deletion" of words and phrases and permitting "*de minimis*" changes. You also cite to a structural argument that, in your view, Congress's grant of "additional authority to add language to an ANDA product's labeling when omitting a protected pediatric use. . . . – and the absence of a similar provision for non-pediatric uses – indicates that FDA does not otherwise have authority to add wording to an ANDA product's labeling in this fashion to ensure the omission of protected uses."[156] We disagree.

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[153] See Entresto Supplement 018 Clinical Review(s) at 17 (PDF 48/176).

[154] See Petition at 23.

[155] See Petition at 19.

[156] See Petition at 18, footnote 73. Here, the petition misconstrues the purpose and the function of 21 USC 355a(o)(2). Contrary to your argument, it is not the purpose of section 355a(o)(2) to "ensure the omission of protected uses." Rather, section 355a(o)(2) requires the inclusion of specific language regarding pediatric patients—separate from the carve-out omitting protected uses—because of Congress's objective "to ensure that drugs used in children are properly studied and labeled for pediatric use." H.R. Rep. No. 107-277, at 20 (2001). The distinct statutory provision to which you attempt to analogize is unique to pediatric information and "allows the [FDA] to require that drugs . . . that omit protected pediatric labeling include a statement that the drug is not labeled for the protected pediatric use and any warnings against unsafe pediatric use," H.R. Rep. No. 107-277, at 38. Specifically, section 355a(o)(2)(B) describes circumstances in which an ANDA must include certain pediatric safety information that would otherwise be carved out as protected because that information is necessary to assure safe use of the product in vulnerable pediatric populations. Section 355a(o)(2)(A) further provides that when protected pediatric information is not necessary to assure safe use of the ANDA or 505(b)(2) application, ANDA and 505(b)(2) sponsors that carve out such information must include a statement that pediatric information is approved for the

Contrary to your arguments, FDA has previously permitted the omission of an indication via a carveout where the only way to omit the protected indication was to add words. For example, for the drug Velcade (bortezomib), the labeling as of Supplement 38 stated:

> **1.2 Mantle Cell Lymphoma**
> VELCADE is indicated for the treatment of patients with mantle cell lymphoma who have received at least 1 prior therapy.[157]

This *second-line* treatment indication was not protected by exclusivity. In Supplement 40, the INDICATIONS AND USAGE section of Velcade's labeling was revised to include an indication for the treatment of patients with mantle cell lymphoma who have not received at least one prior therapy—i.e., to permit *first-line* treatment. Thus, the labeling of Supplement 40 was revised to state:

> **1.2 Mantle Cell Lymphoma**
> VELCADE is indicated for the treatment of patients with mantle cell lymphoma.[158]

In response to a citizen petition submitted on behalf of Millennium Pharmaceuticals, Inc. regarding Velcade (Velcade Citizen Petition), FDA found it appropriate to omit the exclusivity-protected information relating to first-line treatment and retain the nonprotected indication for second-line therapy.[159] However, due to the way the labeling was written, the only way to omit the protected indication was to add words to the labeling. FDA found this approach to not only be consistent with our past practice, but also more consistent with the scope of Velcade's exclusivity, which would effectively have been broadened if FDA accepted the arguments made in the Velcade Citizen Petition.[160]

e. The Agency does not rely on discontinued labeling

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reference product but due to patent or exclusivity, the ANDA or 505(b)(2) product is not labeled with that protected information. This statement helps ensure that practitioners seeking a product approved with pediatric use information know that the listed drug referenced is approved with that information. Because this provision is unique to the pediatric context, it has no bearing on whether and how to carve out protected adult information, nor is it relevant to how to continue to include unprotected adult information in the face of such a carve-out.

[157] Velcade Prescribing Information (August 8, 2014), available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/021602s038lbl.pdf.

[158] Velcade Prescribing Information (October 8, 2014), available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/021602s040lbl.pdf.

[159] FDA Docket No. FDA-2017-P-3672, FDA Response to Citizen Petition regarding Velcade (bortezomib) (November 6, 2017) (Velcade Petition Response) at 14, available at https://www.regulations.gov/document/FDA-2017-P-3672-0022.

[160] Velcade Petition Response at 15.

You assert further that "the [A]gency cannot approve an ANDA proposing to substitute discontinued RLD labeling for the protected use in the currently approved RLD labeling."[161] Contrary to your assertion, the Agency is not relying on discontinued labeling when it approves changes to the indication statement that may reflect or be similar to information from a previously approved labeling, rather the Agency is making changes to the current labeling in accordance with the statutory and regulatory provisions described above permitting an ANDA applicant to omit an indication or other aspect of labeling protected by patent or accorded exclusivity. Notably, you argue that there is only one patient population for the indication statement yet have submitted patent information to FDA describing distinct populations for HFpEF and HFrEF, including the '667 patent, which you argue cannot be carved out of labeling without subjecting HFrEF patients to greater risks.[162] Even putting aside this inconsistency, we disagree that the revised indication is a unified indication with one patient population that cannot be carved out.

As described above, when FDA revised the indication for the Entresto labeling to include "heart failure in adult patients with chronic heart failure" with the indication that the "[b]enefits are most clearly evident in patients with [LVEF] below normal," it was written to be clear and concise. The revised indication added language to recognize that the benefits of the drug's efficacy is most evident in patients with LVEF less than or equal to 40 percent and that the benefit declines as LVEF approaches the normal range. Whether the current labeling uses words to describe patients with both preserved and reduced ejection fraction as one population or two populations is not outcome-determinative in this case. While the Entresto labeling discloses a use protected by the HFpEF Patents, ANDA applicants may submit section viii statements proposing to omit information from the labeling that discloses the use protected by the HFpEF Patents. As discussed in the Agency's response to the Velcade Citizen Petition, the scope of protected information is not broadened due to the writing of labeling in a clear and concise manner.[163] Entresto Supplement 018 revised the labeling in part to describe the patient population in a concise manner, but this revision does not prevent ANDA applicants from carving out information protected by the HFpEF Patents from generic sacubitril and valsartan product labeling.

FDA precedent supports the Agency making modifications to the indication statement even if the labeling as modified resembles a prior indication statement. In the FDA's response to the Velcade Citizen Petition (Velcade Petition Response), the Agency denied a citizen petition requesting that the Agency not approve the proposed ANDA labeling because it relied on "discontinued" labeling.[164] In that case, the Agency had approved a supplement, which modified the indication statement to read "for the treatment of patients with mantle cell lymphoma," revising the previous indication for "the treatment of patients with mantle cell lymphoma who

[161] See Petition at 20.

[162] See Petition at 23–25.

[163] Velcade Petition Response at 15.

[164] See Velcade Petition Response at 13–15.

have received at least 1 prior therapy" (i.e., second-line treatment).[165] In the Velcade Petition Response, the Agency stated that it would be appropriate for ANDA applicants to carve out exclusivity associated with first-line treatment by omitting the first-line mantle cell lymphoma indication and retaining the nonprotected indication for "treatment of patients with mantle cell lymphoma who have received at least 1 prior therapy."[166] You distinguish the Entresto Supplement 018 revisions from the revisions at issue in the Velcade Petition Response because you assert that the indication statement was edited "to describe two mutually exclusive patient populations (first-line mantle cell lymphoma patients and second-line mantle cell lymphoma patients) in a single statement."[167] We disagree. As with the issue discussed in the Velcade Petition Response, carving out the indication for patients who could be categorized as having preserved ejection fraction and retaining the indication for patients with reduced ejection fraction is supported by precedent and is within FDA's authority under the same labeling requirements set forth in the FD&C Act and FDA regulations. And as in the Velcade Petition Response, this decision furthers important policy considerations — the Agency "do[es] not believe it would be appropriate for the scope of [patent protection] for [Entresto] to be broadened due to the writing of labeling in a clear and concise manner."[168]

C. Entresto's Subsection 2.6 Modified Dosing Regimen

You request in the Petition that FDA not approve any ANDAs for generic sacubitril and valsartan tablets referencing Entresto as the RLD that "omit[s] the modified dosing regimen for HFrEF patients not taking an ACE inhibitor or ARB, or who were previously taking low doses of these agents."[169] You contend the '667 patent use code "covers the modified dosing regimen described in [s]ection 2.[6] [of Entresto's labeling],"[170] and that the modified dosing information cannot be omitted from generic sacubitril and valsartan product labeling because the information is necessary for the safe use of Entresto for "adult HFrEF patients and for pediatric HFrEF patients weighing more than 50 kg" who are ACE inhibitor- or ARB-naïve, or who previously received a low dose of these agents.[171] You assert that generic product labeling that omits the modified dosing information would fail to inform health care providers and RAS inhibitor-naïve/low dose patients of the "safest" option for administering sacubitril and valsartan, which you assert "would lead to an increase in clinically significant adverse events for such patients" and "could result in diminished effectiveness if these patients are unable to tolerate the standard starting dose and titration schedule."[172] Finally, you point to Colcrys (colchicine), Xyrem

[165] Velcade Petition Response at 2–3.

[166] Velcade Petition Response at 14–15.

[167] Petition at 21.

[168] Velcade Petition Response at 15.

[169] See, e.g., Petition at 4, 23–30.

[170] See Petition at 23–24.

[171] See Petition at 23–30.

[172] Petition at 4, 23–30.

(sodium oxybate), and Lonsurf (trifluridine and tipiracil) as examples where FDA did not permit ANDAs to omit protected information related to dosing adjustments and argue that the same approach should be followed for ANDAs referencing Entresto as the RLD.[173] Because you believe that ANDAs referencing Entresto as the RLD cannot omit the subsection 2.6 information on the modified dosing regimen for ACE inhibitor- or ARB-naïve/low dose patients, you contend that a section viii statement to the '667 patent is impermissible, and thus any ANDA applicant must address this patent by submitting a certification pursuant to section 505(j)(2)(A)(vii) of the FD&C Act.[174]

After a careful review of the Petition and the administrative record, FDA concludes that omitting patent-protected information concerning a modified dosing regimen for Entresto patients who are ACE inhibitor- or ARB-naïve (or who were previously taking low doses of these agents) from labeling would not render generic sacubitril and valsartan tablets less safe or effective than Entresto for all remaining, nonprotected conditions of use. As explained further below, FDA disagrees with you that generic product labeling must retain the patent-protected modified dosing information in subsection 2.6 of Entresto's labeling. Accordingly, FDA disagrees that a section viii statement to the '667 patent is impermissible because the associated labeling information currently protected by that patent can be omitted without rendering an ANDA drug less safe and effective than Entresto for all remaining, nonprotected conditions of use. Thus, an ANDA applicant need not address this patent by submitting a certification described in section 505(j)(2)(A)(vii) of the FD&C Act. As discussed further below, FDA is denying your request in the Petition related to the '667 patent.

1. Omission of the Subsection 2.6 Modified Dosing Regimen

The omission of the subsection 2.6 modified dosing regimen from the labeling of generic sacubitril and valsartan tablets would not render these drugs less safe or effective than Entresto for the remaining nonprotected conditions of use because the WARNING AND PRECAUTIONS section (section 5) of labeling are sufficient to mitigate the risk of Entresto's important adverse reactions. FDA's regulations permit ANDA applicants to omit from labeling patent-protected conditions of use and obtain approval for the remaining, nonprotected conditions of use, provided that the differences between the RLD and generic drug product labeling would not render the generic drug product less safe or effective than the RLD for the remaining, nonprotected conditions of use.[175] As noted above, in determining how to carve out language from an ANDA's labeling to give effect to the RLD's patent protection, the current labeling of the RLD is examined and any appropriate omissions are made. FDA evaluates any proposed labeling differences between the ANDA labeling and the RLD labeling on a case-by-

[173] See Petition at 26–29.

[174] See Petition at 23.

[175] See generally §§ 314.92(a)(1), 314.94(a)(8)(iv), and 314.127(a)(7).

case basis to determine whether the proposed differences are permissible under the applicable statute and regulations because this inquiry is fact-specific.[176]

You assert that if the modified dosing regimen in subsection 2.6 of Entresto's labeling is omitted from ANDA labeling, relevant HFrEF patients would be dosed under the standard titration schedule provided for in subsection 2.1 of Entresto's labeling. You contend that this would "likely increase the rates of clinically significant adverse events in this patient population and could also result in decreased efficacy, if patients discontinue treatment prematurely or remain on a lower dose before advancing to the labeled target maintenance dose."[177] You therefore argue that the modified dosing regimen is "critical" to inform relevant patients and health care providers of the "safest" and "best-tolerated" option for administering sacubitril and valsartan,[178] and that "[o]mission of the patent-protected information in [s]ection 2.[6] would render an ANDA product less safe and effective than [Entresto] for the remaining conditions of use."[179] While we agree that the TITRATION study informed the modified dosing regimen in section 2.6 of Entresto's labeling, and that such modified dosing regimen is described by the '667 patent use code, we disagree that the modified dosing regimen is necessary for the safe and effective use of sacubitril and valsartan tablets for the remaining nonprotected conditions of use.

Whether the section 2.6 dosing modification is the *safest* and *best-tolerated* option for such patients, as you contend in the Petition, is unknown because initiation using this dosing regimen has only been studied in an uncontrolled manner (i.e., single-blind run-in from TITRATION). As explained above, TITRATION studied 498 HF patients who were randomized to the modified dose (24/26 mg or E50) or standard dose (49/51 mg or E100) regimen. The primary objective of TITRATION was to compare incidences of hypotension, renal dysfunction, hyperkalemia, and angioedema. The study's secondary objective was to compare the proportion of patients achieving a target dose of Entresto. All patients had to tolerate a single-arm run-in with E50, limiting generalizability to truly naïve patients. Notably, the rates of hypotension, renal dysfunction, and hyperkalemia observed in TITRATION were similar between the two groups.[180] As discussed above, TITRATION was a supportive phase 2 trial and suggested that ACEi- or ARB-naïve/low dose patients ***might*** benefit from a slow up-titration regimen with a lower starting dose to increase tolerability and reduce the risk of adverse reactions such as hypotension, hyperkalemia, and renal impairment.[181] Although TITRATION provided some information about the safety profiles of the standard and modified dosing regimens, for example,

[176] FDA has stated that omission of a precaution, warning, or similar information about a condition of use that is not proposed for inclusion in the labeling of a generic drug product can, but does not necessarily, render the generic drug product less safe for its remaining, nonprotected conditions of uses. See, e.g., letter from J. Woodcock, CDER Director, to Philip Honerkamp, Jazz Pharmaceuticals, Inc., Docket No. FDA-2016-P-2672 (January 17, 2017) (Xyrem Petition).

[177] See Petition at 24–25.

[178] See Petition at 25–26.

[179] Petition at 24.

[180] See, e.g., Entresto 2015 Clinical Pharmacology and Biopharmaceutics Review(s) at 16 (PDF 24/53).

[181] See Entresto 2015 Medical Review(s) at 80 (PDF 92/299) (emphasis added); see also at 70 (PDF 82/299).

that more patients were able to achieve and maintain target doses of Entresto with the modified dosing regimen (78 percent versus 84 percent, p = 0.08), the results of TITRATION are not robust.[182] Therefore, while TITRATION supports the dosing recommendation in section 2.6 for ACEi- or ARB-naïve/low dose patients, it does not provide a scientific basis to conclude, as you assert in your Petition, that the standard Entresto dosing regimen puts such patients at a greater risk of adverse reactions or that section 2.6 is "critical" to ensuring the safe and effective use of a generic sacubitril and valsartan product. In addition, other sections of Entresto's labeling describe sufficiently how to mitigate the risk of adverse reactions like hypotension, renal dysfunction, and hyperkalemia, including by using lower doses of Entresto.

We consider other sections of Entresto's prescribing information to be sufficient to ensure that a generic drug product with the proposed labeling carve out is as safe and effective as Entresto for the remaining, nonprotected conditions of use. Even without the protected section 2.6 modified dosing regimen, section 5 of Entresto's prescribing information, specifically subsections 5.3 (Hypotension), 5.4 (Impaired Renal Function), and 5.5 (Hyperkalemia), describes sufficiently how health care providers can manage intolerability or adverse reactions for all patients initiating and up-titrating on Entresto. Indeed, these labeling sections describe sufficiently the need to use lower doses of Entresto to mitigate the risks of hypotension, renal dysfunction, and hyperkalemia.[183] We note that in the studies supporting Entresto's safety and efficacy, treatment with Entresto almost always was preceded by a run-in period with its standard dose to assess tolerability.[184] The Agency believes that health care practitioners are in the best position to determine an appropriate initial dose of Entresto using the information contained in Entresto's labeling, including section 5. We also note that prior to Entresto's initial approval in 2015, published guidelines on HF treatment have supported a general up-titration approach guided by tolerability and do not specify the RAS inhibitor-naïve/low dose group as an at-risk group.[185] So while we agree that premature treatment discontinuation is typically caused by intolerability or

[182] See, e.g., Entresto 2015 Medical Review at 70 (PDF 82/299) (noting that the small number of subjects in TITRATION limits certain interpretation of the data). We note that the recommendation in section 2.6 of Entresto's prescribing information to "initiate pediatric patients weighing 40 to 50 kg who meet this criterion at 0.8 mg/kg twice daily using the oral suspension" is not supported by any direct data but rather reflects an extrapolation of the *halving* of the standard dose in adults.

[183] See Entresto Labeling, subsection 5.3 (Hypotension) (noting the potential need to start at a lower dose); subsection 5.4 (Impaired Renal Function) (noting the potential need to down-titrate); subsection 5.5 (Hyperkalemia) (noting potential need for dosage reduction).

[184] See, e.g., Entresto Labeling, subsection 6.1.

[185] See, e.g., 2013 ACCF/AHA Guideline for Management of Heart Failure: A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, Circulation, 2013, 128(16): e240–e327; and 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines, Circulation, 2022, 145(18):e895–e1032 ("The use of these specific medications for HFrEF should involve initiation at low-starting doses, uptitration at specified intervals as tolerated, and achieving-maintaining the target doses shown to be effective in major clinical trials.").

adverse reactions, FDA believes that section 5 of Entresto's labeling describes sufficiently how to manage those situations, including through dose adjustment of Entresto.

As explained in Entresto's 2015 reviews, FDA believed at that time, and still believes, that the risk of Entresto's important adverse reactions (hypotension, renal dysfunction, and hyperkalemia) can be adequately managed through labeling that describes clinical monitoring and dose titration.[186] FDA has determined as a scientific matter that subsections 5.3, 5.4, and 5.5 are sufficient for this purpose, and that it is not necessary to retain the information for adult patients and for pediatric patients in subsection 2.6 of Entresto's labeling in the labeling for generic sacubitril and valsartan tablets to assure safe and effective use. FDA has also determined that generic sacubitril and valsartan tablets with the patent-protected information on the subsection 2.6 modified dosing regimen carved out remain as safe and effective as Entresto for the remaining nonprotected conditions of use. Accordingly, a carve out of the patent-protected information on the subsection 2.6 modified dosing regimen is permissible in this case.

2. The Agency Precedent Cited in the Petition Is Inapposite

You point to Colcrys (colchicine), Xyrem (sodium oxybate), and Lonsurf (trifluridine and tipiracil) as examples where FDA did not permit ANDAs to omit protected information related to dosing adjustments and argue that the same approach should be followed for ANDAs referencing Entresto as the RLD.[187] We disagree because each example you cite is distinguishable on factual grounds, including because each concerned different considerations and risks associated with different drugs and in different classes, and used to treat different patients for different conditions and therefore are inapposite.

a. Colcrys (colchicine)

One citizen petition response you cite in support of your Petition involved a proposed carve out from the labeling for Colcrys (colchicine).[188] The protected information at issue in the Colcrys citizen petition related to the dosing regimen for colchicine for treatment of acute gout flares. Colcrys qualified for a 3-year period of exclusivity based on a new clinical investigation (the AGREE trial) that was essential to the approval of Colcrys for the treatment of acute gout flares and demonstrated that a lower dose regimen of colchicine for such treatment was as effective as the standard higher dose regimen and resulted in significantly fewer adverse events. Although the 3-year exclusivity was limited to treatment of acute gout flares, FDA considered whether omission of certain labeling information regarding treatment of acute gout flares would render a proposed *duplicate* of Colcrys less safe or effective than Colcrys for prophylaxis of gout flares in the event that a health care provider determined that it was necessary to use colchicine for

[186] Entresto 2015 Clinical Review at 11 (PDF 11/171); see also at 80 ("Overall, [Entresto] has an acceptable safety profile in patients with HfrEF. We believe that the key toxicities of [Entresto] can be managed through proper labeling.")

[187] See Petition at 26–29.

[188] See Petition at 26 (citing FDA Citizen Petition Response regarding Colcrys (colchicine), Docket No. FDA-2010-P-0614-0072 (May 25, 2011), available at https://www.regulations.gov/document/FDA-2010-P-0614-0072).

treatment of an acute gout flare in a patient receiving colchicine for prophylaxis. FDA granted, in part, the petitioner's request.

The circumstances here are different from the circumstances in the Colcrys citizen petition. In the Colcrys citizen petition response, FDA stated that the labeling for a single-ingredient colchicine product seeking approval for prophylaxis of gout flares should inform health care providers that the lower dose colchicine regimen evaluated in the AGREE trial is adequate to treat an acute gout flare that may occur during chronic colchicine use. At that time, information about the lower dose regimen was deemed to be important for minimizing the risk of cumulative toxicity from colchicine.[189] With Entresto, the Agency has no similar certainty regarding the implications of the recommendation provided in subsection 2.6 of Entresto's labeling based on TITRATION or otherwise. As discussed previously, section 5 of Entresto's prescribing information describes sufficiently how health care providers can manage intolerability or adverse reactions for all Entresto patients, and the omission of the protected language in Entresto's labeling would not render a generic sacubitril and valsartan product less safe or effective than Entresto for the remaining, nonprotected condition of use.

b. Xyrem (sodium oxybate)

Another citizen petition response you cite in support of your Petition involved a proposed carve out from the labeling for Xyrem (sodium oxybate).[190] The protected information at issue in the Xyrem citizen petition related to the drug-drug interaction (DDI) with divalproex sodium and resulting dose reduction instructions in the prescribing information and risk evaluation and mitigation strategy for Xyrem. FDA determined that in the absence of the DDI information in certain sections of the Xyrem labeling a prescriber would not know that coadministering divalproex sodium with sodium oxybate would result in a net increase in overall exposure to sodium oxybate such that the initial dose of sodium oxybate should be reduced by at least 20 percent. FDA found that the study conducted by the petitioner provided data to characterize the risk associated with the DDI with divalproex sodium and provided specific dose adjustment recommendations. FDA considered whether omission of certain labeling information regarding the DDI with divalproex sodium and resulting dose reduction instructions would render a proposed generic of Xyrem less safe or effective than Xyrem and granted the petitioner's request.

The circumstances here are different from the circumstances in the Xyrem citizen petition. In the Xyrem citizen petition response, FDA stated that since coadministration of Xyrem and divalproex sodium was shown to increase mean systemic exposure to sodium oxybate by approximately 25 percent, the information about this interaction and the resulting dosing recommendations were important to prevent an exacerbation of potentially life-threatening effects associated with Xyrem. FDA also explained that unlike the general statement in other

[189] FDA subsequently determined, in the context of a single-ingredient colchicine product approved through the 505(b)(2) pathway (Mitigare capsules), that this issue may be addressed by a limitation of use statement in product labeling advising that the safety and effectiveness of Mitigare for acute treatment of gout flares during prophylaxis has not been studied.

[190] See Petition at 27 (citing FDA citizen petition response regarding Xyrem (sodium oxybate), Docket No. FDA-2016-P-2672 (January 17, 2017), available at https://www.regulations.gov/document/FDA-2016-P-2672-0019).

sections of the Xyrem labeling, the specific references to divalproex sodium in certain subsections provided explicit information regarding the nature and extent of the interaction, the potential effects, and specific recommendations regarding dose reduction. With Entresto, the Agency has no similar certainty regarding the implications of the recommendation provided in subsection 2.6 of Entresto's labeling based on TITRATION or otherwise. As discussed previously, section 5 of Entresto's prescribing information describes sufficiently how health care providers can manage intolerability or adverse reactions for all Entresto patients, and the omission of the protected language in Entresto's labeling would not render a generic sacubitril and valsartan product less safe or effective than Entresto for the remaining, nonprotected condition of use.

c. Lonsurf (trifluridine and tipiracil)

Another citizen petition response you cite in support of your Petition involved a proposed carve out from the labeling for Lonsurf (trifluridine and tipiracil).[191] The protected information at issue in the Lonsurf citizen petition related to pharmacokinetic (PK) information for patients with severe renal impairment and related dose reduction recommendations. FDA found that a patient's exposure to trifluridine and tipiracil after taking Lonsurf would vary based on the patient's renal function and that patients with renal impairment could have increased tipiracil exposure leading to increased trifluridine exposure due to increased inhibition of trifluridine metabolism by tipiracil, which may lead to more treatment-limiting severe toxicity. FDA thus required petitioner to conduct a dedicated renal impairment study to determine the appropriate dose of Lonsurf for patients with severe renal impairment. FDA determined that the study results showed that severe renal impairment increased the steady-state area under the receiver operating characteristic curve (dose-normalized) of trifluridine by 2.4-fold. Lonsurf's labeling was updated with information showing that the exposures of Lonsurf's two active ingredients are significantly increased in patients with severe renal impairment and recommended that patients with severe renal impairment may be prescribed the drug under a modified dosing regimen. FDA considered whether omission of certain labeling information regarding dose reduction and related PK information for patients with severe renal impairment would render a proposed generic of Lonsurf less safe or effective than Lonsurf and granted the petitioner's request.

The circumstances here are different from the circumstances in the Lonsurf citizen petition. In the Lonsurf citizen petition response, FDA stated that the petitioner's dedicated PK studies in patients with impaired renal function showed that the exposures of Lonsurf's two active ingredients are significantly increased in patients with severe renal impairment and may lead to more severe toxicity and adverse events. FDA also found that other sections of Lonsurf's prescribing information were insufficient to ensure that a generic drug with the proposed labeling carve out would be as safe as Lonsurf for the remaining, nonprotected conditions of use. With Entresto, the Agency has no similar certainty regarding the implications of the recommendation provided in subsection 2.6 of Entresto's labeling based on TITRATION or otherwise. As discussed previously, section 5 of Entresto's prescribing information describes sufficiently how health care providers can manage intolerability or adverse reactions for all Entresto patients, and

[191] See Petition at 27 (citing FDA citizen petition response regarding Lonsurf (trifluridine and tipiracil), Docket No. FDA-2022-P-0155 (July 22, 2022), available at https://www.regulations.gov/document/FDA-2022-P-0155-0006).

the omission of the protected language in Entresto's labeling would not render a generic sacubitril and valsartan product less safe or effective than Entresto for the remaining, nonprotected condition of use.

Accordingly, we disagree with your assertions that the Agency's decisions in Colcrys, Xyrem, and Lonsurf are determinative of whether it is permissible for an ANDA to carve out the information on a modified dosing regimen in subsection 2.6 of Entresto's labeling.[192] As explained above, FDA's regulations permit ANDA applicants to omit from labeling patent-protected conditions of use and obtain approval for the remaining, nonprotected conditions of use, provided that the differences between the RLD and generic drug product labeling would not render the generic drug product less safe or effective than the RLD for the remaining, nonprotected conditions of use.[193] This is a fact-specific inquiry, and FDA makes these determinations on a case-by-case basis. The Agency has determined that section 5 of Entresto's prescribing information describes sufficiently how health care providers can manage intolerability or adverse reactions for all Entresto patients, and the omission of the protected language in Entresto's labeling would not render a generic sacubitril and valsartan product less safe or effective than Entresto for the remaining, nonprotected condition of use.

IV. CONCLUSION

For the reasons described above, the Petition is denied.

Sincerely,

Douglas C. Throckmorton -S

Digitally signed by Douglas C. Throckmorton -S
Date: 2024.07.24 10:05:00 -04'00'

Patrizia Cavazzoni, M.D.
Director
Center for Drug Evaluation and Research

[192] See, e.g., Letter from J. Woodcock, Director of FDA's CDER, to W. Bertrand, MedImmune Oncology, Inc., Docket No. FDA-2006-P-0274 (March 13, 2008) and Letter from J. Woodcock, Director of FDA's CDER, to E. Lengle, Watson Laboratories, Inc., Docket No. FDA-2008-P-0069 (July 28, 2008) (both noting that FDA has approved generic tramadol products with labeling that excluded a protected, slower titration schedule but included information on the unprotected faster titration schedule also appearing in the labeling of the innovator product); see also Letter from J. Woodcock, Director of FDA's CDER, to A. Bennett, Ropes & Gray, LLP, Docket No. FDA-2006-P-0073 (November 18, 2008) (in part, denying request to require generic budesonide inhalation suspension products to include a once-daily dosing regimen and related information in labeling).

[193] See generally §§ 314.92(a)(1), 314.94(a)(8)(iv), and 314.127(a)(7).