UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF COLUMBIA

NOVARTIS PHARMACEUTICALS CORPORATION, Plaintiff, v. XAVIER BECERRA, in his official capacity as Secretary of Health and Human Services, *et al.*, Defendants, and MSN PHARMACEUTICALS INC., *et al.*, Intervenor-Defendants.	No. 1:24-cv-02234-DLF

Federal Defendants' Opposition to Novartis's Motion for Temporary Restraining Order or Preliminary Injunction

OF COUNSEL:

SAMUEL R. BAGENSTOS
General Counsel
U.S. Department of Health and Human Services

MARK RAZA
Chief Counsel
Food and Drug Administration

WENDY S. VICENTE
Deputy Chief Counsel, Litigation

LEAH A. EDELMAN
Associate Chief Counsel
Office of the Chief Counsel
Food and Drug Administration

BRIAN M. BOYNTON
Principal Deputy Assistant Attorney General

ARUN G. RAO
Deputy Assistant Attorney General

AMANDA N. LISKAMM
Director

LISA K. HSIAO
Senior Deputy Director

HILARY K. PERKINS
Assistant Director

GABRIEL I. SCHONFELD
(D.C. Bar No. 155539)

10903 New Hampshire Ave.
White Oak Building 31
Silver Spring, MD 20993-002

Trial Attorney
Consumer Protection Branch
Civil Division
U.S. Department of Justice
P.O. Box 386
Washington, DC 20044-0386
(202) 353-1531
(202) 514-8742 (fax)
Gabriel.I.Schonfeld@usdoj.gov

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INTRODUCTION

The Federal Food, Drug, and Cosmetic Act (FDCA) strikes a careful balance between protecting the patent rights of brand-name drug companies and promoting consumer access to safe and effective low-cost generics. Although a generic drug usually must have the same labeling as its brand-name predecessor, federal law allows the U.S. Food and Drug Administration (FDA) to approve generic labeling which "carves out" portions of the brand's labeling that describe a patent-protected method of using the drug. FDA will review a proposed carve out under the agency's regulations both to confirm that it corresponds to a patent listed in the agency's "Orange Book," and to ensure that approving it would not make the generic less safe or effective for the remaining non-protected uses. This litigation challenges FDA's straightforward application of the law to approve two labeling changes proposed by Intervenor-Defendants MSN Pharmaceuticals Inc. and MSN Laboratories Private Ltd. ("MSN").

MSN sought FDA approval for generic sacubitril and valsartan, a heart failure medication marketed by Plaintiff Novartis Pharmaceuticals Corp. ("Novartis") under the brand name Entresto®. MSN's application contained two changes from the Entresto® label—the "Use Carve Out" and the "Dosage Carve Out." The Use Carve Out omitted Entresto®'s use for heart failure in some patients with *normal* ejection fraction (a measure of how well the heart is contracting) by adding language specifying that MSN's generic is approved only for heart failure with *reduced* ejection fraction. The Dosage Carve Out omitted instructions for starting a certain subset of patients on a reduced dose of Entresto®. FDA approved MSN's application with both labeling changes, and simultaneously denied a citizen petition that Novartis had filed asking that the agency refuse to do so.

Novartis now seeks a temporary restraining order or preliminary injunction against FDA's approval before MSN is able to launch its generic product in the market.

That motion should be denied because Novartis has not met its burden to show that it is entitled to extraordinary emergency relief.

First, Novartis is not likely to succeed on the merits of its claims. With respect to the Use Carve Out, there is no legal or logical basis for Novartis's claim that generic labeling may only omit a patented use by deleting words from (rather than adding them to) the reference drug's labeling. Rather, the question under the FDCA and FDA's regulations is whether the substance of the change omits a patent-protected use. And with respect to the Dosage Carve Out, Novartis has not shown that FDA acted arbitrarily or capriciously when it applied its scientific expertise to determine that omitting Novartis's patent-protected modified dosing regimen would not make MSN's generic product less safe or effective than Entresto® for its remaining unprotected uses.

Second, Novartis has not shown that it will suffer irreparable harm without emergency relief. Novartis is one of the largest and most profitable pharmaceutical firms in the world. Taking the company's assertions of immediate monetary loss at face value, Novartis has shown that it will lose at most around 5% of its $45 billion in annual sales. That is not the sort of devastating harm that courts in the D.C. Circuit have found to be irreparable.

Third, Novartis has not shown that the balance of harms or the public interest favor an injunction. Novartis has no legitimate interest in enjoining FDA's lawful actions or blocking competition from a lawfully approved generic drug. The public at large and MSN, by contrast, have a substantial interest in vindicating the FDCA's public policy in favor of rapid approval for safe, effective, and low-cost generic drugs.

BACKGROUND

A. Statutory and Regulatory Background

Like any other new drug, a generic drug can be marketed in the United States only with FDA's approval. 21 U.S.C. § 355(a). As relevant here, approval to market a

generic drug may be sought by filing an abbreviated new drug application (ANDA). *Id.* § 355(j).

Because an ANDA relies on FDA's finding that a previously approved drug (the "reference" drug) is safe and effective, *id.* § 355(j)(2)(A)(i); 21 C.F.R. § 314.3(b) (defining "Reference listed drug"), § 314.94(a)(3), the applicant does not have to repeat the studies that established the reference drug's safety and efficacy. Rather, it must show that the generic drug is bioequivalent to the reference drug and has the same active ingredient(s), conditions of use, strength, dosage form, and route of administration. *See* 21 U.S.C. § 355(j)(2)(A)(i)-(iv); 21 C.F.R. § 314.94(a)(4)-(7). A generic drug must also meet quality standards. 21 U.S.C. § 355(j)(2)(A)(vi).

Finally, subject to statutory and regulatory exceptions, the generic and reference drugs must have the same labeling. 21 U.S.C. § 355(j)(2)(A)(v); 21 C.F.R. § 314.94(a)(8). One component of that labeling is the "package insert," which contains detailed information for prescribers about the safe and effective use of the drug. *See* 21 C.F.R. §§ 201.100(d), 314.50(l)(1)(i); *see also* Entresto® Package Insert, ECF No. 1-1 (Novartis Mot. Ex. A); MSN Package Insert (Defs. Opp. Ex. A). This includes information about "indications," "dosages," the "frequency and duration of administration," and any "relevant warnings, hazards . . . and precautions." *See id.* § 201.100(d)(1); *see also id.* §§ 201.56, 201.57.

For present purposes,[1] Novartis's claims turn on whether the Use Carve Out and Dosage Carve Out satisfy the FDCA's exception to the "same labeling" requirement for

[1] Novartis's Complaint also alleges that FDA wrongly determined (in response to a different citizen petition than the one underlying its motion) that MSN's product has the same active ingredient as Entresto®. *See* Compl. ¶¶ 42-47, 72-75. *See also* FDA "Same Active Ingredient" Citizen Petition Response, ECF No. 1-7 (May 28, 2024) (Novartis Mot. Ex. G). On the same day it denied that petition, FDA approved three additional ANDAs referencing Entresto® (ANDA 213676, ANDA 213605, and ANDA 213682), with a fourth (ANDA 214719) approved just over a month later. Novartis's motion, however, does not seek emergency relief based on the agency's denial of the "Same Active Ingredient" Citizen Petition.

"changes [that are] required . . . because the [generic] drug and the [reference] drug are produced or distributed by different manufacturers." 21 U.S.C. § 355(j)(2)(A)(v). This "different manufacturer" exception is codified in FDA's regulations. In relevant part, a generic manufacturer may "omi[t] . . . an indication or other aspect" of the reference drug's labeling that is "protected by patent." 21 C.F.R. § 314.94(a)(8)(iv); *see also id.* § 314.92(a)(1) ("[T]he term 'same as' means identical in . . . conditions of use, except that conditions of use for which approval cannot be granted because of . . . an existing patent may be omitted."), § 314.127(a)(7) (permitting approval of "changes required because . . . aspects of the [reference] drug's labeling are protected by patent"). FDA will not, however, approve labeling changes that "render the [generic] drug product less safe or effective than the [reference] drug for all remaining, nonprotected conditions of use." *Id.* § 314.127(a)(7).

B. The Entresto® Package Insert

Entresto® (sacubitril and valsartan) is a heart failure medication first approved by FDA in 2015. *See generally* Entresto® Approval Letter (July 7, 2015), https://perma.cc/KJ8G-X3RV. Two aspects of the Entresto® package insert are relevant here—its description of the disease the drug is indicated to treat in adults, and its discussion of how prescribers may manage each individual patient's dosage level.

Approved Indication. The Entresto® package insert describes the drug's approved indication for adult patients as follows:

> 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.

Entresto® Package Insert, ECF No. 1-1 at § 1.1. LVEF is "one of many measures of cardiac performance used in clinical practice to diagnos[e] and treat patients with

chronic [heart failure]." FDA 2024 Citizen Petition Response, ECF No. 1-8 at 11 (Novartis Mot. Ex. H). It measures the percentage of the blood in the heart's left ventricle (one of the heart's four chambers) that is pumped out each time that ventricle contracts. *Id.* Normal LVEF is in the range of 52%-72% for men and 54%-74% for women. *Id.* Below-normal LVEF is strong evidence that the heart is not contracting properly. *Id.*

Entresto®'s current indication statement is broader than the one FDA initially approved. The Entresto® package insert originally indicated the drug for treatment of adult "patients with chronic heart failure . . . **and reduced ejection fraction**." *See* 2015 Entresto® Package Insert, ECF No. 1-9 at § 1.1 (Novartis Mot. Ex. I) (emphasis added). That language was based on the scope of the clinical study (the "PARADIGM" trial) submitted to support Entresto®'s effectiveness—which only enrolled patients with LVEF at or below what Novartis described as an "arbitrary . . . cut-point" of 40%. *See* FDA 2024 Citizen Petition Response, ECF No. 1-8 at 14-15 & n.70, 26 (quotation omitted). The entire PARADIGM patient population, in other words, had below-normal LVEF. The original Entresto® package insert accurately reflected that fact by stating that Entresto® was indicated for the same population in which its safety and effectiveness had been established—patients with "*reduced* (or *below normal*)" ejection fraction. *Id.* at 28; *see also id.* at 26 (explaining that in the "clinical setting" the phrase "'[heart failure] and reduced ejection fraction' . . . [means] impaired contraction supported by LVEF data below normal").

Following Entresto®'s initial approval, Novartis completed another clinical study of the drug's effectiveness (the "PARAGON" trial). Unlike PARADIGM, which enrolled only patients with below-normal LVEF, PARAGON enrolled patients with LVEF at or *above* 45%—a criterion which included "patients with mildly reduced LVEF *and* patients with normal LVEF." *Id.* at 18 (emphasis added). PARAGON demonstrated that Entresto® is effective in patients who met that criterion, *id.* at 32-33, but did not as

clearly show a benefit in the subgroup of patients with normal LVEF, *id.* at 30. FDA approved an updated indication statement based on the PARAGON results in early 2021 (the "2021 Supplemental Approval"). That updated statement—which still appears in the current Entresto® package insert—"broadened the indication, in part by dropping [the word] *reduced*," while also adding language "suggest[ing] that [Entresto®] may not be effective at the upper range of LVEF." *Id.* at 31. The relevant differences between the original and current Entresto® adult indication statements are shown below:

Original Entresto® Indication Statement	**Current Entresto® Indication Statement**
ENTRESTO is indicated to reduce the risk of cardiovascular death and hospitalization for heart failure in patients with chronic heart failure . . . and reduced ejection fraction. 2015 Entresto® Package Insert, ECF No. 1-9 at § 1.1.	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 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.** Entresto® Package Insert, ECF No. 1-1 at § 1.1.

Dose Management. Multiple portions of the Entresto® package insert instruct prescribers that based on their clinical judgment, they may manage the risk of adverse events by prescribing a reduced dose of the drug. As relevant here, Section 2.6 of the package insert addresses patients who immediately prior to starting Entresto® are not taking, or are taking only low doses of, two types of medication—angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs)—that have a similar effect on the circulatory system as does 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 . . . to follow the recommended dose escalation thereafter.

Entresto® Package Insert, ECF No. 1-1 at § 2.6. This modified dosing regimen is based on the results of another study (the "TITRATION" study) that Novartis submitted to support the safety and tolerability of Entresto®. FDA 2024 Citizen Petition Response, ECF No. 1-8 at 15-16. TITRATION compared 1) patients who initially received 100mg of Entresto® twice daily, increased to 200mg over two weeks, with 2) patients who initially received 50mg of Entresto® twice daily, increased to 200mg over five weeks. *Id.* at 16. Before being assigned to one of those two groups, all participants in TITRATION were required to tolerate taking 50mg twice daily for one week. *Id.* at 16, 40.

Both groups studied in TITRATION experienced similar rates of Entresto®'s most common adverse events, *id.* at 40, and "FDA determined that . . . [the study] showed that Entresto® was well tolerated . . . following *either* a condensed or conservative [dosing] regimen[]," *id.* at 16 (emphasis added). The agency also noted, however, that patients who before TITRATION were not taking (or were taking a low dose of) an ACE inhibitor or ARB "were better able to achieve and maintain the target dose" of Entresto® if their dose increased more gradually, "whereas the rate of [increase] was less important in patients who were taking higher pre-study doses" of an ACE inhibitor or ARB. *Id.* at 16.

Based on those results, FDA concluded that Novartis's proposed modified dosing regimen was "reasonable" because it "*may* reduce the risk" of three adverse events—low blood pressure, kidney impairment, and excess potassium levels—"in patients previously on a low dose of an [ACE inhibitor] or ARB." *Id.* at 16, 40-41

(emphasis added) (quotations omitted); *see also id.* at 16 n. 83 ("The results of . . . TITRATION[] suggest[] that patients who were previously on [a] low dose of [ACE inhibitors or] . . . ARBs *might* benefit from a slow up-titration regimen . . . to increase tolerability and reduce the risk of adverse events . . . .") (emphasis added) (quotations omitted).

Section 2.6, however, is not the Entresto® package insert's only instruction on managing risk by reducing dosage. Section 5 of the insert—"Warnings and Precautions"—independently advises prescribers that the risk of low blood pressure, kidney impairment, and excess potassium levels may be mitigated with a reduced initial dose of Entresto®. The same three risks also underlie TITRATION's addition of section 2.6 to the labeling—so even if the modified dosing regimen in 2.6 is carved out, the continued inclusion of these risks and generalized mitigation recommendations ensures that such labeling is not less safe and effective than the reference drug for the remaining nonprotected conditions of use. The risk of low blood pressure (hypotension) may be managed by "start[ing] at a lower dose." Entresto® Package Insert, ECF No. 1-1 at § 5.3. Kidney (renal) impairment may be addressed by "down-titrat[ing]" (lowering) a patient's dosage. *Id.* § 5.4. And "[d]osage reduction . . . may be required" to address the risk of excess potassium levels (hyperkalemia). *Id.* § 5.5. Moreover, "published guidelines on [heart failure] treatment" show that even before Entresto®'s approval, best clinical practice had long "supported a general up-titration approach guided by tolerability" and did not treat patients with no (or only a low-dose) history of ACE-inhibitor or ARB use "as an at-risk group." FDA 2024 Citizen Petition Response, ECF No. 1-8 at 41 & n.185.

C. Novartis's Listed Patents and Citizen Petition

In the months following the 2021 Supplemental Approval, Novartis submitted the four patents relevant to its motion to FDA for listing in *Approved Drug Products with Therapeutic Equivalence Evaluations*—more commonly known as the "Orange Book." *See*

FDA, *Patent and Exclusivity for NDA N207620*, https://www.accessdata.fda.gov/scripts/cder/ob/patent_info.cfm?Product_No=002&Appl_No=207620&Appl_type=N (last visited Aug. 6, 2024).

The Orange Book is an FDA publication which lists patents covering approved drugs. For "method-of-use" patents—which protect a method of using a drug product rather than a feature of the product itself—the Orange Book includes a description of the claimed use called a "use code." *See generally Caraco Pharm. Lab'ys, Ltd. v. Novo Nordisk A/S*, 566 U.S. 399, 405-07 (2012). Three of the four patents relevant here (the "Use Patents") are listed in the Orange Book for "Treatment of Heart Failure with Preserved Ejection Fraction" (use code U-3084). *See* FDA 2024 Citizen Petition Response, ECF No. 1-8 at 21 (citing U.S. Patents Nos. 9,517,226; 9,937,143; and 11,135,192). The fourth patent (the "Dosage Patent") is listed for "Treating Chronic Heart Failure With Reduced Ejection Fraction in Patients Not 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" (use code U-3170). *See id.* at 21-22 (citing U.S. Patent No. 11,058,667).

Subject to other requirements not at issue here, a generic manufacturer may include in its ANDA a "section viii statement" regarding a method-of-use patent listed in the Orange Book. A section viii statement explains that "the labeling for the [proposed generic drug] . . . does not include [the] indication or other condition of use that is covered by" the patent's listed use code. 21 C.F.R. § 314.94(a)(12)(iii)(A); *see also* 21 U.S.C. § 355(j)(2)(A)(viii). "If the ANDA applicant follows this route, it will propose labeling for the generic drug that 'carves out' from the brand's approved label the still-patented methods of use." *Caraco Pharm.*, 566 U.S. at 406 (quotation omitted). As discussed above, "FDA may approve such a modified label as an exception to the usual rule that a generic drug must bear the same label as the brand-name product." *Id.* (quotation omitted); *see also supra* at 2-4.

After Novartis submitted the last of the Use Patents to be listed in the Orange Book, it submitted a citizen petition to FDA asking that the agency refuse to approve any ANDA that referenced Entresto® and contained a section viii statement regarding either the Use Patents or the Dosage Patent.[2] *See* Novartis 2022 Citizen Petition, ECF No. 1-6 (Novartis Mot. Ex. F). FDA denied Novartis's petition on July 24, 2024. *See generally* FDA 2024 Citizen Petition Response, ECF No. 1-8.

D. MSN's ANDA and Carved Out Labeling

MSN submitted its ANDA for generic sacubitril and valsartan in 2019. *See* MSN ANDA Approval Letter at 1 (July 24, 2024) (Defs. Opp. Ex. B). FDA approved the MSN ANDA on the same day it denied Novartis's citizen petition. *Id.* As approved, MSN's ANDA includes section viii statements regarding both the Use Patents and the Dosage Patent. *Id.* Those statements correspond with two labeling changes (or "carve outs") omitting uses covered[3] by Novartis's patent claims.

[2] Novartis initially submitted a citizen petition raising these issues on November 30, 2021. *See* Novartis 2021 Citizen Petition., Dkt. No. FDA-2021-P-1286-0001 (Nov. 30, 2021). But FDA denied that petition on threshold grounds unrelated to the merits of Novartis's present claims. *See* FDA 2022 Citizen Petition Response, Dkt. No. FDA-2021-P-1286-0014 (April 29, 2022). Novartis renewed its requests several months later in the substantively identical citizen petition underlying this lawsuit.

[3] Here and throughout this memorandum, description of a use as being "covered," "protected," "claimed," or similar by a listed patent refers only to the fact that it is within the use code listed in the Orange Book. FDA does not "independently assess [a] patent's scope or otherwise look behind" the listed use code. *Caraco Pharm.*, 566 U.S. at 406. The agency's "role with respect to patent listing is ministerial," *id.* at 407. (quotation omitted), and FDA takes no position on the scope or validity of the underlying patents themselves. Novartis has asserted its patent rights for the Use Patents and Dosage Patent against MSN and others. *See, e.g., Novartis Pharms. Corp. v. MSN Pharms. Inc., et al*, No. 1:22-cv-1395 (D. Del.). On August 2, 2024, Novartis moved for a preliminary injunction against MSN in its pending patent litigation. *Id.*, ECF No. 213. The court will hold a hearing regarding that motion at 9:00 AM on August 9, 2024.

The Use Carve Out. To exclude the use covered by the Use Patents—"treatment of heart failure with preserved ejection fraction"—the MSN package insert modifies Entresto®'s adult indication statement as follows:

Entresto® Package Insert	MSN Package Insert
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. Entresto® Package Insert, ECF No. 1-1 at § 1.1.	Sacubitril and valsartan tablets are 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 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. MSN Package Insert at § 1.1 (Defs. Opp. Ex. A).

The Dosage Carve Out. To carve out the use protected by the Dosage Patent—"treating chronic heart failure with reduced ejection fraction in patients not 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"—MSN's labeling omits Section 2.6 of the Entresto® package insert entirely:

Entresto® Package Insert	MSN Package Insert
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	N/A *See* MSN Package Insert §§ 2.4-.7 (Defs. Opp. Ex. A).

weeks in adults . . . to follow the recommended dose escalation thereafter. Entresto® Package Insert, ECF No. 1-1 at § 2.6.	

LEGAL STANDARDS

Temporary Restraining Order or Preliminary Injunction. Interim injunctions are "an extraordinary form of judicial relief" that courts grant "sparingly" and only where "the movant, by a clear showing, carries the burden of persuasion." *Biovail Corp. v. FDA*, 519 F. Supp. 2d 39, 43-44 (D.D.C. 2007) (quotations omitted). To obtain preliminary injunctive relief, Novartis has the burden of showing (1) that it is likely to succeed on the merits of its claims, (2) that it is likely to suffer irreparable harm without preliminary relief, (3) that the balance of equities favors an injunction, and (4) that an injunction is in the public interest. *Winter v. Nat. Res. Def. Council, Inc.*, 555 U.S. 7, 20 (2008). Where a federal agency is the defendant, the last two factors merge. *See Am. Immigr. Council v. DHS*, 470 F. Supp. 3d 32, 36 (D.D.C. 2020).

Administrative Procedure Act Claims. The agency in an APA case is entitled to prevail on the merits when its actions were consistent with the APA's standard of review. *Coal. for Common Sense in Gov't Procurement v. United States*, 821 F. Supp. 2d 275, 280 (D.D.C. 2011). The question is whether the challenged action was "arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law." 5 U.S.C. § 706(2)(A). In applying the highly deferential arbitrary-and-capricious standard, the reviewing court may not "substitute its judgment for that of the agency," *Citizens to Pres. Overton Park, Inc. v. Volpe*, 401 U.S. 402, 416 (1971), but must instead uphold the agency's action if it is "rational, based on consideration of the relevant factors and within the scope of the authority delegated to the agency by the statute," *Motor Vehicle Mfrs. Ass'n of U.S., Inc. v. State Farm Mut. Auto. Ins. Co.*, 463 U.S. 29, 42-43 (1983).

ARGUMENT

I. Novartis Has No Likelihood of Success on the Merits.

Novartis challenges both the Use Carve Out and the Dosage Carve Out. *First*, it argues that the Use Carve Out is not permitted by the "different manufacturer" exception to the FDCA's "same labeling" requirement for generic drugs approved under an ANDA. *See* ECF No. 3-1 at 14-21 ("Novartis TRO Mem."). *Second*, Novartis argues that FDA arbitrarily and capriciously determined that the Dosage Carve Out would not make MSN's product less safe and effective than Entresto®. *See id.* at 21-25. Novartis has no likelihood of success on either claim.

A. The Use Carve Out Lawfully Omits a Patent-Protected Use by Adding Language Which Excludes It.

FDA's approval of the Use Carve Out is a straightforward application of the FDCA and FDA regulations—one that has long been upheld by the D.C. Circuit. *See Bristol-Myers Squibb Co. v. Shalala*, 91 F.3d 1493, 1499-1500 (D.C. Cir. 1996).[4] FDA regulations explicitly provide that under the "different manufacturer" exception, the agency may approve an ANDA based on labeling that differs from the reference drug's because it "omi[ts] an indication or other aspect of labeling protected by patent." 21 C.F.R. § 314.94(a)(8)(iv); *see also* 21 C.F.R. § 314.127(a)(7) (FDA may approve an ANDA with labeling differences "required . . . because aspects of the [reference] drug's labeling are protected by patent").

The approved Entresto® adult indication is protected by the Use Patents to the extent that it includes the drug's use in some patients with *normal* ejection fraction. *See* Entresto® Package Insert, ECF No. 1-1 at § 1.1 ("ENTRESTO is indicated . . . in adult patients with chronic heart failure. Benefits are most clearly evident in patients with [LVEF] below normal."); *see also* FDA 2024 Citizen Petition Response, ECF No. 1-8 at 32

[4] Novartis's reliance on *PLIVA, Inc. v. Mensing*, 564 U.S. 604, 614 (2011), is misplaced. *See* Novartis TRO Mem. at 16. Although *Mensing* recognized the general rule that generic labeling must be the same as the brand labeling, 564 U.S. at 612–13, it does not address the exception to that rule for changes due to patent protection.

(explaining that this indication statement "includes patients who could be categorized within prevailing definitions" of heart failure with preserved ejection fraction). MSN's approved labeling omits that protected portion of the Entresto® indication statement by specifying that MSN's product is used only in patients with *reduced* ejection fraction. *See* MSN Package Insert at § 1.1 (Defs. Opp. Ex. A) ("Sacubitril and valsartan tablets are indicated . . . in adult patients with chronic heart failure and reduced ejection fraction."). An indication statement limited to patients with reduced ejection fraction omits Entresto®'s patent-protected use in some patients with normal ejection fraction. So on its face, the Use Carve Out falls within the "different manufacturer" exception to the "same labeling" requirement.

Novartis argues that FDA's approval of the Use Carve Out was nevertheless unlawful for five reasons. None of those arguments have any likelihood of success.

First, Novartis asserts that MSN's ANDA violates the FDCA and FDA regulations because it carves out Entresto®'s patent-protected use in some patients with normal ejection fraction by "adding [a] new" reference to reduced ejection fraction—rather than by "merely omitting language" from the Entresto® indication statement. Novartis TRO Mem. at 18-20. That argument fails because the plain text of the FDCA allows FDA to approve "changes required . . . because the [generic] drug and the [reference] drug are produced or distributed by different manufacturers," with no proviso that those changes may only be accomplished by deleting language. 21 U.S.C. § 355(j)(2)(A)(v). Furthermore, the FDA regulation in question allows FDA to approve the "omission of an *indication or other aspect of labeling*," not omission of *particular words*. 21 C.F.R. § 314.94(a)(8)(iv) (emphasis added).

That is precisely what FDA did here. Entresto® was originally indicated for treating chronic heart failure in patients with reduced ejection fraction. Novartis subsequently broadened the indication statement to include a patent-protected use in some patients with normal ejection fraction. In approving MSN's ANDA, FDA allowed

MSN to modify the Entresto® labeling to omit the patent-protected use and retain the non-protected uses, just as the agency's regulations permit. FDA precedent further confirms that Novartis's position is simply not the law. *See* FDA 2024 Citizen Petition Response, ECF No. 1-8 at 35-36 (agency may approve labeling that restricts scope of indication by adding words), at 37-38 (agency may approve labeling that carves out patent-protected subset of indicated use even if original indication statement did not explicitly describe subset(s)).

The fact that Novartis's position lacks any textual grounding is reason enough to reject it, but not the only one. Novartis's argument—that a generic manufacturer may only omit a patent-protected use by deleting words rather than adding them—puts form over substance and leads to absurd results. A necessary implication of Novartis's position is that the approvability of an ANDA with carved-out labeling would depend on essentially stylistic wording choices in the reference labeling—for example, the choice to draft a concise indication statement rather than one which lists every possible subgroup of patients a subsequent ANDA applicant may seek to omit. But this is not the question posed by the text of either the FDCA or FDA's regulations, which ask whether a labeling change is required because the generic and reference drugs are made by different manufacturers, including whether that difference requires omission of a patent-protected indication or other aspect of labeling. *See* 21 U.S.C. § 355(j)(2)(A)(v); 21 C.F.R. § 314.94(a)(8)(iv).

Second, Novartis asserts that because the Entresto® labeling has "just one indication statement," the Use Carve Out amounts to "rewriting" an indication rather than "omitting" one. Novartis TRO Mem. at 20. Novartis's argument is beside the point because neither the FDCA nor its implementing regulations state that FDA is limited to approving the omission of an "indication." The statute refers broadly to labeling "changes,"21 U.S.C. § 355(j)(2)(A)(v), and FDA's regulations expressly permit changes made to omit "an indication *or other aspect of labeling protected by patent*," 21 C.F.R.

§ 314.94(a)(8)(iv) (emphasis added). The Use Carve Out changes Entresto®'s indication statement to omit its instruction that the drug may be used in at least some patients with normal ejection fraction. Whether that method of use is an "indication" or not is irrelevant—at the very least, it is an "aspect of labeling protected by patent" that may lawfully be omitted from MSN's labeling. *See id.*

Third, Novartis argues that FDA misapplied the "same labeling" requirement by approving a package insert that in certain respects "reverts to the original" Entresto® labeling by carving out an approved use (in some patients with normal ejection fraction) that was added after Entresto®'s initial approval in 2015. Novartis TRO Mem. at 16-18. Novartis is flatly incorrect to assert that FDA relied on an earlier version of Entresto® labeling as "the basis" for assessing whether MSN's ANDA satisfied the "same labeling" requirement. *See id.* Rather, it approved labeling for MSN's generic product that is the same as the current Entresto® labeling except for certain discrete changes that use the current labeling as a baseline and are "in accordance with the statutory and regulatory provisions . . . permitting an ANDA applicant to omit an indication or other aspect of labeling protected by patent." *See* FDA 2024 Citizen Petition Response, ECF No. 1-8 at 37-38. Novartis does not identify any statutory or regulatory basis to prevent FDA from approving an ANDA with otherwise-lawful labeling changes merely because "the labeling as modified resembles a prior indication statement" for the reference drug. *See id.*

Fourth, Novartis argues that even if FDA followed its own regulations in approving the Use Carve Out, doing so exceeded the statutory scope of the "different manufacturer" exception to the FDCA's "same labeling" requirement. Novartis TRO Mem. at 18-19. In Novartis's view, the "'different manufacturer' exception would permit differences in generic labeling [only] to identify a different manufacturer, product name, or company address," and does not allow FDA to "carve out any indications at all." *Id.* at 19 (discussing 21 U.S.C. § 355(j)(2)(A)(v)).

The D.C. Circuit rejected Novartis's argument nearly thirty years ago in *Bristol-Myers Squibb Co. v. Shalala*, 91 F.3d 1493 (D.C. Cir. 1996), when it held that the "different manufacturer" exception "permits [FDA] to approve an ANDA . . . even though the label of the generic product will not include one or more indications that appear on the label of the [reference] drug upon which the ANDA is based." *Bristol-Myers Squibb*, 91 F.3d at 1499-1500. After reviewing in detail the text, structure, and legislative history of the relevant FDCA provisions, the D.C. Circuit agreed with FDA that the agency may approve an ANDA which carves out a patented indication. *Id.* at 1500; *see also Caraco Pharm.*, 566 U.S. at 406 (explaining that a section viii statement allows a generic company to carve out a patent-protected use). *Bristol-Myers Squibb* is directly on point and this Court is bound to apply it.[5]

Fifth, Novartis claims that in approving the Use Carve Out, FDA arbitrarily and capriciously adopted a "strictly quantitative approach" under which sacubitril and valsartan are indicated based on "specific, quantified ejection fraction metrics." Novartis TRO Mem. at 20-21. That is incorrect.

Novartis's argument rests on its assertion that "reduced ejection fraction" is synonymous with "LVEF of less than or equal to 40%," *see id.* at 6, but no such numeric cutoff appears in MSN's approved labeling (or has ever appeared in any version of Entresto®'s labeling). Nor has FDA ever defined "reduced ejection fraction" to refer only to patients with LVEF less than or equal to 40%. *See generally* FDA 2024 Citizen

[5] The Supreme Court's recent decision to overturn the *Chevron* doctrine, *see Loper Bright Enterprises v. Raimondo*, 144 S. Ct. 2244 (2024), does not undermine *Bristol-Myers Squibb* for two reasons. First and most fundamentally, the D.C. Circuit in *Bristol-Myers Squibb* did not *defer* to FDA's statutory interpretation. It *agreed* with the agency's view at the first step of the now-overruled *Chevron* analysis—holding based on its own independent assessment of the statute that "Congress ha[d] directly addressed the issue . . . in dispute." *Bristol-Myers Squibb*, 91 F.3d at 1499-1500. Second, even if the holding of *Bristol-Myers Squibb* had been based on deference to an agency interpretation under *Chevron*, the Supreme Court has made clear that "prior cases that relied on the *Chevron* framework" to hold "that specific agency actions are lawful" are "still subject to statutory *stare decisis* despite [*Loper Bright*'s] change in interpretive methodology." *Loper Bright*, 144 S. Ct. 2244 at 2273.

Petition Response, ECF No. 1-8 at 11-12, 28. FDA has explained that the term simply "reflects the clinical setting of impaired contraction supported by LVEF data below normal," and that the term's inclusion in the original Entresto® labeling "did not restrict the [drug] . . . strictly to patients with LVEF less than or equal to 40 percent." *Id.* at 26-27; *see also id.* at 11-13. Whether or not it would be arbitrary and capricious to approve a heart failure treatment indicated by a numerical LVEF cutoff is irrelevant because FDA did no such thing.

B. FDA Reasonably Determined That the Dosage Carve Out Would Not Compromise Safety or Effectiveness.

FDA's approval of the Dosage Carve Out was not arbitrary or capricious because the agency has provided a reasoned scientific basis for concluding that it will not render MSN's generic product less safe and effective for its remaining conditions of use. *See generally* 21 C.F.R. § 314.127(a)(7). That "scientific judgment within [FDA's] area of expertise" is entitled to a "high level of deference" from this Court, *Rempfer v. Sharfstein*, 583 F.3d 860, 897 (D.C. Cir. 2009) (quotations omitted), and Novartis has shown no likelihood that it will succeed in demonstrating otherwise.

The primary basis for FDA's judgment is that the "WARNINGS AND PRECAUTIONS section ([S]ection 5) of [the MSN] labeling are sufficient to mitigate the risk of [sacubitril and valsartan]'s important adverse reactions." FDA 2024 Citizen Petition Response, ECF No. 1-8 at 39. That means that "[e]ven without the protected [S]ection 2.6 modified dosing regimen . . . , subsections 5.3 ([low blood pressure]), 5.4 ([kidney impairment]), and 5.5 ([excess blood potassium]), describe[] sufficiently how health care providers can manage intolerability or adverse reactions for all patients initiating and up-titrating on [sacubitril and valsartan]. Indeed, these labeling sections describe sufficiently the need to use lower doses . . . to mitigate th[ese] risks . . . ." *Id.* at 41. Particularly where "published guidelines on [heart failure] treatment" have long advised clinicians to use "a general up-titration approach guided by tolerability" and

have not specified the patients addressed by Section 2.6 "as an at-risk group," FDA concluded that "health care practitioners are in the best position to determine an appropriate initial dose of [sacubitril and valsartan] using the information contained in [MSN's] labeling, including [S]ection 5." *Id.* at 41-42. Novartis offers two responses, but neither has any likelihood of success on the merits.

First, Novartis points to the TITRATION study which supported the inclusion of Section 2.6 in the Entresto® package insert. *See generally* Novartis TRO Mem. at 23-25; *see also supra* at 6-8 (discussing TITRATION). Novartis argues that TITRATION establishes that Section 2.6 is "critical safety information," *id.* at 21, because its modified dosing regimen is the "safest and best-tolerated option" for patients not previously taking, or taking only a low dose of, an ACE inhibitor or ARB, *id.* at 24. That is incorrect because notwithstanding the TITRATION results, "[w]hether the [S]ection 2.6 dosing modification is the *safest* and *best-tolerated* option for such patients . . . is unknown." FDA 2024 Citizen Petition Response, ECF No. 1-8 at 40.

Novartis overstates TITRATION's significance. Since 2015, FDA has maintained that TITRATION at most suggests that some patients *might* benefit from the modified regimen that Section 2.6 describes. *Id.* at 16 & n.83, 40 & n.181. FDA's review of TITRATION determined that although it "provided some information about the safety profiles of the standard and modified dosing regimens[,] . . . [TITRATION's results] are not robust," and "do[] not provide a scientific basis to conclude . . . that the standard Entresto® dosing regimen puts [the relevant group of] patients at a greater risk of adverse reactions or that [S]ection 2.6 is 'critical' to ensuring . . . safe and effective use." *Id.* at 40-41. That is enough to conclude that the regimen Novartis proposed is "*reasonable*," *id.* 16 & n.83 (emphasis added)—but not to show that it is *required.*

Second, Novartis misunderstands FDA's basis for determining that other portions of the MSN labeling are adequate to ensure safety and efficacy following the Dosage Carve Out. FDA has determined based on its expertise that "health practitioners are in

the best position to determine an appropriate *initial* dose" of MSN's product. *See* FDA 2024 Citizen Petition Response, ECF No. 1-8 at 41 (emphasis added). In prescribing MSN's product for its remaining non-protected uses, healthcare providers will be able to consider not only the information contained in Section 5 of the MSN package insert, but also "published guidelines on [heart failure] treatment" that "support[] a general up-titration approach guided by tolerability," as well as their own clinical experience. *Id.* To be sure, some of the language in Section 5 refers to dosage modification after an adverse reaction has already occurred, but FDA is not relying on that language taken in isolation. The agency's consideration of published treatment guidelines and the experienced judgment of individual prescribers is a facially reasonable application of FDA's scientific expertise, and there is no likelihood that Novartis will succeed in arguing that the agency's decision was arbitrary and capricious.

II. Novartis's Allegations of Purely Economic Injury Do Not Establish Irreparable Harm.

Novartis's motion should also be denied for failure to meet the D.C. Circuit's "high standard for irreparable injury." *See Chaplaincy of Full Gospel Churches v. England*, 454 F.3d 290, 297 (D.C. Cir. 2006). Failure to show irreparable harm is an independent ground for denying interim injunctive relief "even if the other three factors . . . merit [it]." *Id.*

At the outset, the core of Novartis's alleged injuries—whether framed in terms of revenue loss, loss of market position in general, exposure to generic competition in particular, or potential shrinkage of the Entresto® business unit in response to lowered demand—is a claim that Novartis will make less money from Entresto® if and when MSN enters the market. But "[i]n the D.C. Circuit, mere economic loss does not, in and of itself, constitute irreparable harm. Monetary loss, even irretrievable monetary loss, may constitute irreparable harm only if it is so severe as to cause extreme hardship to the business or threaten its very existence." *Mylan Lab'ys Ltd. v. FDA*, 910 F. Supp. 2d

299, 313 (D.D.C. 2012) (quotations omitted); *see also Watson Lab'ys, Inc. v. Sebelius*, 2012 WL 13076147, at *3 (D.D.C. Oct. 23, 2012) ("[E]ven unrecoverable economic losses do not constitute irreparable harm . . . if they do not spell financial disaster for the moving party"); *Wisc. Gas Co. v. FERC*, 758 F.2d 669 (D.C. Cir. 1985) ("Mere injuries, however substantial, in terms of money, time and energy . . . are not enough.") (quotations omitted).

Novartis has not shown that the losses it fears would so *immediately* threaten the *very existence* of its business as to merit a temporary restraining order issued on an extraordinarily compressed timeline. Novartis is one of the largest pharmaceutical firms in the world. Last year, its annual global sales revenue of approximately $45 billion generated about $8.5 billion in profit. *See* Novartis AG FY2023 Annual Report at 43 (Jan. 31, 2024), https://perma.cc/G6RP-3LDY. Approximately $3 billion of Novartis's annual revenue is from sales of Entresto® in the United States. *Id.* at 46. Novartis asserts that 80% of those sales—$2.4 billion—would be lost within six months of MSN's entry into the market. Declaration of Kristin Miller, ECF No. 3-2 at ¶ 24. Novartis's worst-case near-term loss, in other words, would amount to only 5.3% of its $45 billion in annual sales revenue. That is not nearly enough to establish irreparable harm. *See, e.g.*, *Varicon Int'l v. Office of Personnel Mgmt.*, 934 F. Supp. 440, 447-48 (D.D.C. 1996) (no irreparable harm from loss of contract representing 10% of plaintiff's revenue); *TGS Tech., Inc. v. Dept. of Air Force*, 1992 WL 19058, at *3-4 (D.D.C. Jan. 14, 1992) (no irreparable harm from loss of contract constituting 20% of plaintiff's business); *Arrow Air, Inc. v. United States*, 649 F. Supp. 993, 995 (D.D.C. 1986) (no irreparable harm from loss of contract representing 25% of plaintiff's revenue). Novartis "will undoubtably survive as a going business concern absent injunctive relief." *Bristol-Myers Squibb Co. v. Shalala*, 923 F. Supp. 212, 220-21 (D.D.C. 1996).

Importantly, it makes no difference to the above analysis that FDA enjoys sovereign immunity from suit for money damages. *Cf.* Novartis TRO Mem. at 27. As

one of Novartis's own authorities explains, alleged damages "do not become *per se* irreparable" because they are barred by sovereign immunity. *Xiaomi Corp. v. Dept. of Defense*, 2021 WL 950144, at *10 (D.D.C. Mar. 12, 2021). "To hold otherwise would essentially eviscerate the irreparable harm requirement for any cases brought against the government." *Id.*

Novartis's three other theories of irreparable harm are as unavailing as its claim of purely economic injury:

First, Novartis vaguely suggests that a reduction in revenue from Entresto® might constrain its ability to invest in the research and development on which its future as a company depends. *See* Miller Declaration, ECF No. 3-2 at ¶¶ 33, 37. Notably, Novartis does not assert that if MSN enters the market Novartis would *actually* reduce its research expenditures. Rather, it alleges only that they would be "jeopardized." *Id.* But there is no reason at all to credit that claim. Novartis makes about $8.5 billion in profit per year. *See* Novartis AG FY2023 Annual Report at 43. So even if 100% of the $2.4 billion in Entresto® sales that Novartis expects to lose would otherwise have been spent directly on research, the company could replace those losses dollar-for-dollar from other revenue streams and still have more than $6 billion in profit to spare. Novartis's ability to fund its research efforts plainly does not depend on its ability to maintain its current level of Entresto® sales.

Second, Novartis speculates that if a generic version of Entresto® is approved (and particularly a generic version with carved-out labeling), consumers and prescribers might confuse the generic with Entresto® itself and damage the reputation of Novartis's product. *See* Miller Declaration, ECF No. 3-2 at ¶¶ 34, 39-41. Courts in this district have repeatedly rejected essentially indistinguishable conjecture as a basis for injunctive relief. *See, e.g.*, Prelim. Inj. Mot. Hr'g Tr., ECF No. 36 at 39:11-40:6, *Vanda Pharms., Inc. v. FDA*, No. 1:23-cv-280-TSC (D.D.C. Mar. 6, 2023) (Defs. Opp. Ex. C) ("For Vanda to suffer meaningful reputational harm, a significant portion of patients would

have to . . . One, switch [to the generic] . . . ; two, make a mistake in using [the generic] as a result of [labeling differences]; three, suffer harm as a result; and four, irrationally blame that harm on Vanda rather than [the generic manufacturer]."); *Biovail Corp. v. FDA*, 448 F. Supp. 2d 154, 164-65 (D.D.C. 2006) (rejecting speculation that the "negative impact" of adverse reactions to a new generic product "will inevitably reach [the brand] as well"); *Astellas Pharma US, Inc. v. FDA*, 642 F. Supp. 2d 10, 23 (D.D.C. 2009) (rejecting speculation that brand-name firm "will suffer a loss of goodwill and reputation . . . to the extent that the generic product fails to provide the safe and effective treatment that physicians have come to expect from [the brand-name drug]").

Third, Novartis argues that it faces irreparable harm from the loss of "statutory rights of patent and market exclusivity." Novartis TRO Mem. at 26. But Novartis may not claim irreparable harm from the loss of rights it is not actually suing to enforce. Novartis claims in its complaint that FDA unlawfully approved the labeling changes proposed in MSN's ANDA. It does not, by contrast, claim that the agency denied Novartis any statutory market exclusivity or infringed the company's patent rights. Nor could it. Novartis has already enjoyed a full period of regulatory exclusivity for which it was qualified, *see* FDA 2024 Citizen Petition Response, ECF No. 1-8 at 6, 23, and is already seeking to vindicate its patent rights in the appropriate forum—an infringement suit against MSN rather than APA litigation against FDA, *see generally Novartis Pharms. Corp. v. MSN Pharms. Inc., et al.*, No. 1:22-cv-1395 (D. Del.).

III. Neither the Balance of Harms Nor the Public Interest Favor an Injunction.

Denying an injunction will not cause Novartis any irreparable injury. As discussed in detail above, FDA acted lawfully in approving MSN's ANDA, and Novartis will not suffer more than ordinary economic loss if and when MSN enters the market. Novartis has no legitimate interest either in enjoining lawful agency action or in avoiding competitive pressure from a lawfully approved generic drug.

By contrast, granting an injunction would inflict tremendous harm on the public at large and MSN. Where, as here, FDA followed the law in approving MSN's ANDA and found it to meet all applicable approval standards, there is a clear "public interest in receiving generic competition to brand-name drugs as soon as possible." *Astellas Pharma*, 642 F. Supp. 2d at 23-24 (quotation omitted). There is no legitimate contrary interest on which an injunction could rest. Simply put, "[t]he public interest factor is inextricably linked with the merits of [Novartis's] claim and, accordingly, provides [it] no support." *Id.* at 23 (citing *Serono Lab'ys, Inc. v. Shalala*, 158 F.3d 1313, 1326 (D.C. Cir. 1998)). An injunction would also deprive MSN of its ability under the FDCA to market its approved generic drug. The balance of harms and public interest factors tip decisively against injunctive relief.

CONCLUSION

For these reasons, the Court should deny Novartis's motion for a temporary restraining order or preliminary injunction.

August 6, 2024

Respectfully submitted,
/s/ Gabriel I. Schonfeld

GABRIEL I. SCHONFELD
(D.C. Bar. No. 155539)
Trial Attorney
Consumer Protection Branch
Civil Division
U.S. Department of Justice
PO Box 386
Washington, DC 20044-0386
(202) 353-1531
(202) 514-8742 (fax)
Gabriel.I.Schonfeld@usdoj.gov

Exhibit A

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use SACUBITRIL AND VALSARTAN TABLETS safely and effectively. See full prescribing information for SACUBITRIL AND VALSARTAN TABLETS.

SACUBITRIL AND VALSARTAN tablets, for oral use

Initial U.S. Approval: 2015

WARNING: FETAL TOXICITY

See full prescribing information for complete boxed warning.

- **When pregnancy is detected, discontinue sacubitril and valsartan tablets as soon as possible. (5.1)**
- **Drugs that act directly on the renin-angiotensin system can cause injury and death to the developing fetus. (5.1)**

----------RECENT MAJOR CHANGES----------

- Dosage and Administration. (2.3) 4/2024

----------INDICATIONS AND USAGE----------

Sacubitril and valsartan tablets are a combination of sacubitril, a neprilisin inhibitor, and valsartan, an angiotensin II receptor blocker, and 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. (1.1)
- for the treatment of symptomatic heart failure with systemic left ventricular systolic dysfunction in pediatric patients aged one year and older. Sacubitril and valsartan tablets reduces NT-proBNP and is expected to improve cardiovascular outcomes. (1.2)

----------DOSAGE AND ADMINISTRATION----------

- The recommended starting dosage for adults is 49 mg/51 mg orally twice daily. The target maintenance dose is 97 mg/103 mg orally twice daily. (2.2)
- Adjust adult doses every 2 to 4 weeks to the target maintenance dose, as tolerated by the patient. (2.2)
- For pediatric patients, see the Full Prescribing Information for recommended dosage, titrations, preparation and administration instructions. (2.3, 2.4)
- Reduce starting dose to half the usually recommended starting dosage for:
  - patients with severe renal impairment (2.7)
  - patients with moderate hepatic impairment (2.8)

----------DOSAGE FORMS AND STRENGTHS----------

- Film-coated tablets: 24/26 mg; 49/51 mg; 97/103 mg (3)

----------CONTRAINDICATIONS----------

- Hypersensitivity to any component. (4)
- History of angioedema related to previous ACEi or ARB therapy. (4)
- Concomitant use with ACE inhibitors. (4, 7.1)
- Concomitant use with aliskiren in patients with diabetes. (4, 7.1)

----------WARNINGS AND PRECAUTIONS----------

- Observe for signs and symptoms of angioedema and hypotension. (5.2, 5.3)
- Monitor renal function and potassium in susceptible patients. (5.4, 5.5)

----------ADVERSE REACTIONS----------

Adverse reactions occurring greater than or equal to 5% are hypotension, hyperkalemia, cough, dizziness, and renal failure. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact MSN Pharmaceuticals Inc. at 1-855-668-2369 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------

- Avoid concomitant use with aliskiren in patients with estimated glomerular filtration rate (eGFR) less than 60. (7.1)
- Potassium-sparing diuretics: May lead to increased serum potassium. (7.2)
- Nonsteroidal Anti-Inflammatory Drugs (NSAIDs): May lead to increased risk of renal impairment. (7.3)
- Lithium: Increased risk of lithium toxicity. (7.4)

----------USE IN SPECIFIC POPULATIONS----------

- Lactation: Breastfeeding not recommended. (8.2)
- Severe Hepatic Impairment: Use not recommended. (2.8, 8.6)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 07/2024

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: FETAL TOXICITY

- **When pregnancy is detected, discontinue sacubitril and valsartan tablets as soon as possible *(5.1)***
- **Drugs that act directly on the renin-angiotensin system can cause injury and death to the developing fetus *(5.1)***

1 INDICATIONS AND USAGE

1.1 Adult Heart Failure

Sacubitril and valsartan tablets are indicated to reduce the risk of cardiovascular death and hospitalization for heart failure in adult patients with chronic heart failure and reduced ejection fraction.

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

1.2 Pediatric Heart Failure

Sacubitril and valsartan tablets are indicated for the treatment of symptomatic heart failure with systemic left ventricular systolic dysfunction in pediatric patients aged one year and older. Sacubitril and valsartan tablets reduces NT-proBNP and is expected to improve cardiovascular outcomes.

2 DOSAGE AND ADMINISTRATION

2.1 General Considerations

Sacubitril and valsartan tablets are contraindicated with concomitant use of an angiotensin-converting enzyme (ACE) inhibitor. If switching from an ACE inhibitor to sacubitril and valsartan tablets allow a washout period of 36 hours between administration of the two drugs *[see Contraindications (4) and Drug Interactions (7.1)]*.

2.2 Adult Heart Failure

The recommended starting dose of sacubitril and valsartan tablet is 49/51 mg orally twice-daily.

Double the dose of sacubitril and valsartan tablets after 2 to 4 weeks to the target maintenance dose of 97/103 mg twice daily, as tolerated by the patient.

2.3 Pediatric Heart Failure

For the recommended dosage for pediatric patients aged 1 year and older, refer to Table 1 if using the tablets.

Take the recommended dose orally twice daily. Adjust pediatric patient doses every 2 weeks, as tolerated by the patient.

Table 1: Recommended Dose and Titration for Pediatric Patients Using Tablets

	Titration Step Dose (twice daily)		
	Starting	**Second**	**Final**
Less than 40 kg[†]	1.6 mg/kg	2.3 mg/kg	3.1 mg/kg
At least 40 kg, less than 50 kg	24 mg/26 mg	49 mg/51 mg	72 mg/78 mg[‡]
At least 50 kg	49 mg/51 mg	72 mg/78 mg[‡]	97 mg/103 mg

[†] Use of the oral suspension recommended in these patients. Recommended mg/kg doses are of the combined amount of both sacubitril and valsartan *[see Dosage and Administration (2.4)]*.

[‡] Doses of 72 mg/78 mg can be achieved using three 24 mg/26 mg tablets *[see Dosage Forms and Strengths (3)]*.

2.4 Preparation of Oral Suspension Using Tablets

Sacubitril and valsartan tablets oral suspension can be substituted at the recommended tablet dosage in patients unable to swallow tablets.

Sacubitril and valsartan tablets 800 mg/200 mL oral suspension can be prepared in a concentration of 4 mg/mL (sacubitril/valsartan 1.96/2.04 mg/mL). Use sacubitril and valsartan tablets 49/51 mg tablets in the preparation of the suspension.

To make an 800 mg/200 mL (4 mg/mL) oral suspension, transfer eight tablets of sacubitril and valsartan tablets 49/51 mg film-coated tablets into a mortar. Crush the tablets into a fine powder using a pestle. Add 60 mL of Ora-Plus® into the mortar and triturate gently with pestle for 10 minutes, to form a uniform suspension. Add 140 mL of Ora-Sweet® SF into mortar and triturate with pestle for another 10 minutes, to form a uniform suspension. Transfer the entire contents from the mortar into a clean 200 mL amber colored PET or glass bottle. Place a press-in bottle adapter and close the bottle with a child resistant cap.

The oral suspension can be stored for up to 15 days. Do not store above 25°C (77°F) and do not refrigerate. Shake before each use.

*Ora-Sweet SF® and Ora-Plus® are registered trademarks of Paddock Laboratories, Inc.

2.7 Dose Adjustment for Severe Renal Impairment

In adults and pediatric patients with severe renal impairment estimated glomerular filtration rate (eGFR less than 30 mL/min/1.73 m^2), start sacubitril and valsartan tablets at half the usually recommended starting dose. After initiation, increase the dose to follow the recommended dose escalation thereafter *[see Dosage and Administration (2.2, 2.3)]*.

Note: Initiate pediatric patients weighing 40 to 50 kg who meet this criterion at 0.8 mg/kg twice daily using the oral suspension *[see Dosage and Administration (2.3, 2.4)]*.

No starting dose adjustment is needed for mild or moderate renal impairment.

2.8 Dose Adjustment for Hepatic Impairment

In adults and pediatric patients with moderate hepatic impairment (Child-Pugh B classification), start sacubitril and valsartan tablets at half the usually recommended starting dose. After initiation, increase the dose to follow the recommended dose escalation thereafter *[see Dosage and Administration (2.2, 2.3)]*.

Note: Initiate pediatric patients weighing 40 to 50 kg who meet this criterion at 0.8 mg/kg twice daily using the oral suspension *[see Dosage and Administration (2.3, 2.4)]*.

No starting dose adjustment is needed for mild hepatic impairment.

Use in patients with severe hepatic impairment is not recommended.

3 DOSAGE FORMS AND STRENGTHS

Sacubitril and valsartan tablets are supplied as unscored, oval shaped, film-coated tablets in the following strengths:

Sacubitril and valsartan tablets 24/26 mg, (sacubitril 24 mg and valsartan 26 mg) are purple colored, oval shaped, biconvex, film coated tablets one side debossed with 'M' and other side debossed with 'S1' and free from physical defects.

Sacubitril and valsartan tablets 49/51 mg, (sacubitril 49 mg and valsartan 51 mg) are light yellow colored, oval shaped, biconvex, film coated tablets one side debossed with 'M' and other side debossed with 'S2' and free from physical defects.

Sacubitril and valsartan tablets 97/103 mg, (sacubitril 97 mg and valsartan 103 mg) are light pink to pink colored, oval shaped, biconvex, film coated tablets one side debossed with 'M' and other side debossed with 'S3', free from physical defects.

4 CONTRAINDICATIONS

Sacubitril and valsartan is contraindicated:

- in patients with hypersensitivity to any component
- in patients with a history of angioedema related to previous ACE inhibitor or ARB therapy *[see Warnings and Precautions (5.2)]*
- with concomitant use of ACE inhibitors. Do not administer within 36 hours of switching from or to an ACE inhibitor *[see Drug Interactions (7.1)]*
- with concomitant use of aliskiren in patients with diabetes *[see Drug Interactions (7.1)]*

5 WARNINGS AND PRECAUTIONS

5.1 Fetal Toxicity

Sacubitril and valsartan can cause fetal harm when administered to a pregnant woman. Use of drugs that act on the renin-angiotensin system during the second and third trimesters of pregnancy reduces fetal renal function and increases fetal and neonatal morbidity and death. When pregnancy is detected, consider alternative drug treatment and discontinue sacubitril and valsartan. However, if there is no appropriate alternative to therapy with drugs affecting the renin-angiotensin system, and if the drug is considered lifesaving for the mother, advise a pregnant woman of the potential risk to the fetus *[see Use in Specific Populations (8.1)]*.

5.2 Angioedema

Sacubitril and valsartan may cause angioedema *[see Adverse Reactions (6.1)]*. If angioedema occurs, discontinue sacubitril and valsartan immediately, provide appropriate therapy, and monitor for airway compromise. Sacubitril and valsartan must not be re-administered. In cases of confirmed angioedema where swelling has been confined to the face and lips, the condition has generally resolved without treatment, although antihistamines have been useful in relieving symptoms.

Angioedema associated with laryngeal edema may be fatal. Where there is involvement of the tongue, glottis or larynx, likely to cause airway obstruction, administer appropriate therapy, e.g., subcutaneous epinephrine/adrenaline solution 1:1000 (0.3 mL to 0.5 mL) and take measures necessary to ensure maintenance of a patent airway.

Sacubitril and valsartan has been associated with a higher rate of angioedema in Black than in non-Black patients.

Patients with a prior history of angioedema may be at increased risk of angioedema with sacubitril and valsartan *[see Adverse Reactions (6.1)]*. Sacubitril and valsartan must not be used in patients with a known history of angioedema related to previous ACE inhibitor or ARB therapy *[see Contraindications (4)]*. Sacubitril and valsartan should not be used in patients with hereditary angioedema.

5.3 Hypotension

Sacubitril and valsartan 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 sacubitril and valsartan 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 sacubitril and valsartan. 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 sacubitril and valsartan *[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 sacubitril and valsartan 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, sacubitril and valsartan 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 sacubitril and valsartan *[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 sacubitril and valsartan may be required *[see Dosage and Administration (2.7)]*.

6 ADVERSE REACTIONS

Clinically significant adverse reactions that appear in other sections of the labeling include:

- Angioedema *[see Warnings and Precautions (5.2)]*
- Hypotension *[see Warnings and Precautions (5.3)]*
- Impaired Renal Function *[see Warnings and Precautions (5.4)]*
- Hyperkalemia *[see Warnings and Precautions (5.5)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Adult Heart Failure

In PARADIGM-HF, patients were required to complete sequential enalapril and sacubitril and valsartan run-in periods of (median) 15 and 29 days, respectively, prior to entering the randomized double-blind period comparing sacubitril and valsartan and enalapril. During the enalapril run-in period, 1,102 patients (10.5%) were permanently discontinued from the study, 5.6% because of an adverse event, most commonly renal dysfunction (1.7%), hyperkalemia (1.7%) and hypotension (1.4%). During the sacubitril and valsartan run-in period, an additional 10.4% of patients permanently discontinued treatment, 5.9% because of an adverse event, most commonly renal dysfunction (1.8%), hypotension (1.7%) and hyperkalemia (1.3%). Because of this run-in design, the adverse reaction rates described below are lower than expected in practice.

In the double-blind period, safety was evaluated in 4,203 patients treated with sacubitril and valsartan and 4,229 treated with enalapril. In PARADIGM-HF, patients randomized to sacubitril and valsartan received treatment for up to 4.3 years, with a median duration of exposure of 24 months; 3,271 patients were treated for more than one year. Discontinuation of therapy because of an adverse event during the double-blind period occurred in 450 (10.7%) of sacubitril and valsartan treated patients and 516 (12.2%) of patients receiving enalapril.

Adverse reactions occurring at an incidence of greater than or equal to 5% in patients who were treated with sacubitril and valsartan in the double-blind period of PARADIGM-HF are shown in Table 3.

In PARADIGM-HF, the incidence of angioedema was 0.1% in both the enalapril and sacubitril and valsartan run-in periods. In the double-blind period, the incidence of angioedema was higher in patients treated with sacubitril and valsartan than enalapril (0.5% and 0.2%, respectively). The incidence of angioedema in Black patients was 2.4% with sacubitril and valsartan and 0.5% with enalapril *[see Warnings and Precautions (5.2)]*.

Orthostasis was reported in 2.1% of patients treated with sacubitril and valsartan compared to 1.1% of patients treated with enalapril during the double-blind period of PARADIGM-HF. Falls were reported in 1.9% of patients treated with sacubitril and valsartan compared to 1.3% of patients treated with enalapril.

Table 3: Adverse Reactions Reported in greater than or equal to 5% of Patients Treated with Sacubitril and Valsartan in the Double-Blind Period of PARADIGM-HF

	Sacubitril and Valsartan (n = 4,203) %	**Enalapril (n = 4,229) %**
Hypotension	18	12
Hyperkalemia	12	14
Cough	9	13
Dizziness	6	5
Renal failure/acute renal failure	5	5

Pediatric Heart Failure

The adverse reactions observed in pediatric patients 1 year to less than 18 years old who received treatment with sacubitril and valsartan were consistent with those observed in adult patients.

Laboratory Abnormalities

Hemoglobin and Hematocrit

Decreases in hemoglobin/hematocrit of greater than 20% were observed in approximately 5% of both sacubitril and valsartan- and enalapril-treated patients in the double-blind period in PARADIGM-HF.

Serum Creatinine

During the double-blind period in PARADIGM-HF, approximately 16% of both sacubitril and valsartan- and enalapril-treated patients had increases in serum creatinine of greater than 50%.

Serum Potassium

During the double-blind period of PARADIGM-HF, approximately 16% of both sacubitril and valsartan- and enalapril-treated patients had potassium concentrations greater than 5.5 mEq/L.

6.2 Postmarketing Experience

The following additional adverse reactions have been reported in postmarketing experience. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Hypersensitivity including rash, pruritus, and anaphylactic reaction

7 DRUG INTERACTIONS

7.1 Dual Blockade of the Renin-Angiotensin-Aldosterone System

Concomitant use of sacubitril and valsartan with an ACE inhibitor is contraindicated because of the increased risk of angioedema *[see Contraindications (4)]*.

Avoid use of sacubitril and valsartan with an ARB, because sacubitril and valsartan contains the angiotensin II receptor blocker valsartan.

The concomitant use of sacubitril and valsartan with aliskiren is contraindicated in patients with diabetes *[see Contraindications (4)]*. Avoid use with aliskiren in patients with renal impairment (eGFR less than 60 mL/min/1.73 m^2).

7.2 Potassium-Sparing Diuretics

As with other drugs that block angiotensin II or its effects, concomitant use of potassium-sparing diuretics (e.g., spironolactone, triamterene, amiloride), potassium supplements, or salt substitutes containing potassium may lead to increases in serum potassium *[see Warnings and Precautions (5.5)]*.

7.3 Nonsteroidal Anti-Inflammatory Drugs (NSAIDs) Including Selective Cyclooxygenase-2 Inhibitors (COX-2 Inhibitors)

In patients who are elderly, volume-depleted (including those on diuretic therapy), or with compromised renal function, concomitant use of NSAIDs, including COX-2 inhibitors, with sacubitril and valsartan may result in worsening of renal function, including possible acute renal failure. These effects are usually reversible. Monitor renal function periodically.

7.4 Lithium

Increases in serum lithium concentrations and lithium toxicity have been reported during concomitant administration of lithium with angiotensin II receptor antagonists. Monitor serum lithium levels during concomitant use with sacubitril and valsartan.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Sacubitril and valsartan can cause fetal harm when administered to a pregnant woman. Use of drugs that act on the renin-angiotensin system during the second and third trimesters of pregnancy reduces fetal renal function and increases fetal and neonatal morbidity and death (*see Clinical Considerations*). Most epidemiologic studies examining fetal abnormalities after exposure to antihypertensive use in the first trimester have not distinguished drugs affecting the renin-angiotensin system from other antihypertensive agents. In animal reproduction studies, sacubitril and valsartan treatment during organogenesis resulted in increased embryo-fetal lethality in rats and rabbits and teratogenicity in rabbits (*see Data*). When pregnancy is detected, consider alternative drug treatment and discontinue sacubitril and valsartan. However, if there is no appropriate alternative to therapy with drugs affecting the renin-angiotensin system, and if the drug is considered lifesaving for the mother, advise a pregnant woman of the potential risk to the fetus.

The background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Clinical Considerations

Fetal/Neonatal Adverse Reactions

Oligohydramnios in pregnant women who use drugs affecting the renin-angiotensin system in the second and third trimesters of pregnancy can result in the following: reduced fetal renal function leading to anuria and renal failure, fetal lung hypoplasia, skeletal deformations, including skull hypoplasia, hypotension, and death.

Perform serial ultrasound examinations to assess the intra-amniotic environment. Fetal testing may be appropriate, based on the week of gestation. Patients and physicians should be aware, however, that oligohydramnios may not appear until after the fetus has sustained irreversible injury. If oligohydramnios is observed, consider alternative drug treatment. Closely observe neonates with histories of *in utero* exposure to sacubitril and valsartan for hypotension, oliguria, and hyperkalemia. In neonates with a history of *in utero* exposure to sacubitril and valsartan, if oliguria or hypotension occurs, support blood pressure and renal perfusion. Exchange transfusions or dialysis may be required as a means of reversing hypotension and replacing renal function.

Data

Animal Data

Sacubitril and valsartan treatment during organogenesis resulted in increased embryo-fetal lethality in rats at doses greater than or equal to 49 mg sacubitril/51 mg valsartan/kg/day (less than or equal to 0.06 [LBQ657, the active metabolite] and 0.72 [valsartan]-fold the maximum recommended human dose [MRHD] of 97/103 mg twice-daily on the basis of the area under the plasma drug concentration-time curve [AUC]) and rabbits at doses greater than or equal to 5 mg sacubitril/5 mg valsartan/kg/day (2-fold and 0.03-fold the MRHD on the basis of valsartan and LBQ657 AUC, respectively). Sacubitril and valsartan is teratogenic based on a low incidence of fetal hydrocephaly, associated with maternally toxic doses, which was observed in rabbits at a sacubitril and valsartan dose of greater than or equal to 5 mg sacubitril/5mg valsartan/kg/day. The adverse embryo-fetal effects of sacubitril and valsartan are attributed to the angiotensin receptor antagonist activity.

Pre- and postnatal development studies in rats at sacubitril doses up to 750 mg/kg/day (2.2-fold the MRHD on the basis of LBQ657 AUC) and valsartan at doses up to 600 mg/kg/day (0.86-fold the MRHD on the basis of AUC) indicate that treatment with sacubitril and valsartan during organogenesis, gestation and lactation may affect pup development and survival.

8.2 Lactation

Risk Summary

There is no information regarding the presence of sacubitril/valsartan in human milk, the effects on the breastfed infant, or the effects on milk production. Sacubitril/valsartan is present in rat milk (*see Data*). Because of the potential for serious adverse reactions in breastfed infants from exposure to sacubitril/valsartan, advise a nursing woman that breastfeeding is not recommended during treatment with sacubitril and valsartan.

Data

Following an oral dose (15 mg sacubitril/15 mg valsartan/kg) of [^{14}C] sacubitril and valsartan to lactating rats, transfer of LBQ657 into milk was observed. After a single oral administration of 3 mg/kg [^{14}C] valsartan to lactating rats, transfer of valsartan into milk was observed.

8.4 Pediatric Use

The safety and effectiveness of sacubitril and valsartan have been established for the treatment of heart failure in pediatric patients 1 year to less than 18 years. Use of sacubitril and valsartan was evaluated in a multinational, randomized, double-blind trial comparing sacubitril and valsartan and enalapril in 375 patients aged 1 month to less than 18 years (sacubitril and valsartan n = 187; Enalapril n = 188) (PANORAMA-HF) *[see Clinical Studies (14.2)]*. The safety profile in pediatric patients (1 year to less than 18 years) receiving sacubitril and valsartan was similar to that seen in adult patients.

Limited safety and efficacy data in patients aged 1 month to less than 1 year were inadequate to support conclusions on safety and efficacy in this age group.

Juvenile Animal Toxicity Data

Sacubitril given orally to juvenile rats from postnatal day (PND) 7 to PND 35 or PND 70 (an age approximately equivalent to neonatal through pre-pubertal development or adulthood in humans) at doses greater than or equal to 400 mg/kg/day (approximately 2-fold the AUC exposure to the active metabolite of sacubitril, LBQ657, at an sacubitril and valsartan pediatric clinical dose of 3.1 mg/kg twice daily) resulted in decreases in body weight, bone length, and bone mass. The decrease in body weight was transient from PND 10 to PND 20 and the effects for most bone parameters were reversible after treatment stopped. Exposure at the No-Observed-Adverse-Effect-Level (NOAEL) of 100 mg/kg/day was approximately 0.5-fold the AUC exposure to LBQ657 at the 3.1 mg/kg twice daily dose of sacubitril and valsartan. The mechanism underlying bone effects in rats and the translatability to pediatric patients are unknown.

Valsartan given orally to juvenile rats from PND 7 to PND 70 (an age approximately equivalent to neonatal through adulthood in humans) produced persistent, irreversible kidney damage at all dose levels. Exposure at the lowest tested dose of 1 mg/kg/day was approximately 0.2-fold the exposure at 3.1 mg/kg twice daily dose of sacubitril and valsartan based on AUC. These kidney effects in neonatal rats represent expected exaggerated pharmacological effects that are observed if rats are treated during the first 13 days of life. This period coincides with 36 weeks of gestation in humans, which could occasionally extend up to 44 weeks after

Sacubitril and Valsartan Tablets

DXXXXXX-XX

Patient Information
Sacubitril and Valsartan (sak ue' bi tril and val sar' tan) tablets

What is the most important information I should know about Sacubitril and Valsartan Tablets?

Sacubitril and Valsartan Tablets can harm or cause death to your unborn baby. Talk to your doctor about other ways to treat heart failure if you plan to become pregnant. Tell your doctor right away if you become pregnant during treatment with Sacubitril and Valsartan Tablets.

What are Sacubitril and Valsartan Tablets?

Sacubitril and Valsartan Tablets are a prescription medicine used to treat:

- adults with long-lasting (chronic) heart failure to help reduce the risk of death and hospitalization. Sacubitril and Valsartan Tablets works better when the heart cannot pump a normal amount of blood to the body.
- certain children 1 year of age and older who have symptomatic heart failure.

It is not known if Sacubitril and Valsartan Tablets are safe and effective in children under 1 year of age.

Do not take Sacubitril and Valsartan Tablets if you:

- are allergic to any of the ingredients in Sacubitril and Valsartan Tablets. See the end of this Patient Information leaflet for a complete list of ingredients in Sacubitril and Valsartan Tablets.
- have had an allergic reaction, including swelling of your face, lips, tongue, throat, or trouble breathing while taking a type of medicine called an angiotensin-converting enzyme (ACE) inhibitor or angiotensin II receptor blocker (ARB).
- take an ACE inhibitor medicine. **Do not take Sacubitril and Valsartan Tablets for at least 36 hours before or after you take an ACE inhibitor medicine**. Talk with your doctor or pharmacist before taking Sacubitril and Valsartan Tablets if you are not sure if you take an ACE inhibitor medicine.
- have diabetes and take a medicine that contains aliskiren.

Before taking Sacubitril and Valsartan Tablets, tell your doctor about all of your medical conditions, including if you:

- have a history of hereditary angioedema
- have kidney or liver problems
- have diabetes
- are pregnant or plan to become pregnant. See **"What is the most important information I should know about Sacubitril and Valsartan Tablets?"**
- are breastfeeding or plan to breastfeed. It is not known if Sacubitril and Valsartan passes into your breast milk. You should not breastfeed during treatment with Sacubitril and Valsartan Tablets. You and your doctor should decide if you will take Sacubitril and Valsartan Tablets or breastfeed.

Tell your doctor about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. Taking Sacubitril and Valsartan Tablets with certain other medicines may affect each other. Taking Sacubitril and Valsartan Tablets with other medicines can cause serious side effects. Especially tell your doctor if you take:

- potassium supplements or a salt substitute
- nonsteroidal anti-inflammatory drugs (NSAIDs)
- lithium
- other medicines for high blood pressure or heart problems such as an ACE inhibitor, ARB, or aliskiren

Keep a list of your medicines to show your doctor and pharmacist when you get a new medicine.

How should I take Sacubitril and Valsartan Tablets?

- Take Sacubitril and Valsartan Tablets exactly as your doctor tells you to take it.
- Take Sacubitril and Valsartan Tablets 2 times each day. Your doctor may change your dose of Sacubitril and Valsartan Tablets during treatment.
- If you or your child cannot swallow tablets, or if tablets are not available in the prescribed strength, you or your child may take Sacubitril and Valsartan tablets prepared as a liquid (oral) suspension.
- If you or your child switches between taking the Sacubitril and Valsartan tablet and the liquid suspension prepared from Sacubitril and Valsartan Tablets, your doctor will adjust the dose as needed.
- **If you or your child are prescribed Sacubitril and Valsartan Tablets to be prepared as a liquid suspension:**
  - Your pharmacist will prepare Sacubitril and Valsartan tablets for you or your child to take as a liquid suspension.
  - Shake the bottle of suspension well before measuring the dose of medicine and before taking or giving the dose.
- If you miss a dose, take it as soon as you remember. If it is close to your next dose, do not take the missed dose. Take the next dose at your regular time.
- If you take too much Sacubitril and Valsartan, call your doctor right away.

What are the possible side effects of Sacubitril and Valsartan Tablets?

Sacubitril and Valsartan Tablets may cause serious side effects including:

- See **"What is the most important information I should know about Sacubitril and Valsartan Tablets?"**

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(b) (4)

- **Serious allergic reactions causing swelling of your face, lips, tongue, and throat (angioedema) that may cause trouble breathing and death.** Get emergency medical help right away if you have symptoms of angioedema or trouble breathing. Do not take Sacubitril and Valsartan Tablets again if you have had angioedema during treatment with Sacubitril and Valsartan Tablets.
- People who are Black and take Sacubitril and Valsartan Tablets may have a higher risk of having angioedema than people who are not Black and take Sacubitril and Valsartan Tablets.
- People who have had angioedema before taking Sacubitril and Valsartan Tablets may have a higher risk of having angioedema than people who have not had angioedema before taking Sacubitril and Valsartan Tablets. See **"Who should not take Sacubitril and Valsartan Tablets?"**
- **Low blood pressure (hypotension).** Low blood pressure is common during treatment with Sacubitril and Valsartan Tablets. Your risk of low blood pressure is greater if you also take water pills (diuretics). Call your doctor if you become dizzy or lightheaded, or you develop extreme tiredness (fatigue).
- **Kidney problems.** Kidney problems are common during treatment with Sacubitril and Valsartan Tablets and can be serious and can lead to kidney failure. Your doctor will check your kidney function during your treatment with Sacubitril and Valsartan Tablets.
- **Increased amount of potassium in your blood (hyperkalemia).** Increased blood potassium levels are common during treatment with Sacubitril and Valsartan Tablets . Your doctor will check your potassium blood level during your treatment with Sacubitril and Valsartan Tablets .

The most common side effects of Sacubitril and Valsartan Tablets also include cough and dizziness.

Your doctor may need to lower your dose, temporarily stop treatment, or permanently stop treatment if you develop certain side effects or if you have changes in your kidney function or increased blood levels of potassium during treatment with Sacubitril and Valsartan Tablets.

These are not all of the possible side effects of Sacubitril and Valsartan Tablets. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store Sacubitril and Valsartan Tablets?

- Store Sacubitril and Valsartan Tablets at room temperature between 68°F to 77°F (20°C to 25°C).
- Protect Sacubitril and Valsartan tablets from moisture.
- Store bottles of Sacubitril and Valsartan tablets prepared as an oral suspension at room temperature less than 77°F (25°C) for up to 15 days. **Do not** refrigerate Sacubitril and Valsartan tablets prepared as an oral suspension.

Keep Sacubitril and Valsartan Tablets and all medicines out of the reach of children.

General information about the safe and effective use of Sacubitril and Valsartan Tablets

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use Sacubitril and Valsartan Tablets for a condition for which it was not prescribed. Do not give Sacubitril and Valsartan Tablets to other people, even if they have the same symptoms that you have. It may harm them.

You can ask your pharmacist or doctor for information about Sacubitril and Valsartan Tablets that is written for health professionals.

What are the ingredients in Sacubitril and Valsartan Tablets?

Active ingredients: sacubitril and valsartan

Inactive ingredients: colloidal silicon dioxide, crospovidone, croscarmellose sodium, magnesium stearate, microcrystalline cellulose and talc. The film-coat inactive ingredients are hypromellose, titanium dioxide, macrogol, talc and iron oxide red. The film-coat for the 24 mg of sacubitril and 26 mg of valsartan tablet and the 97 mg of sacubitril and 103 mg of valsartan tablet also contains iron oxide black. The film-coat for the 49 mg of sacubitril and 51 mg of valsartan tablet also contains iron oxide yellow.

Prepared sacubitril and valsartan oral suspension also contains Ora-Sweet SF® and Ora-Plus.®.

All brand names listed are the registered trademarks of their respective owners.

Manufactured by:
MSN Laboratories Private Limited
Telangana – 509 228,
INDIA

Distributed by:
MSN Pharmaceuticals Inc.
Piscataway, NJ 08854 -3714

For more information, go to www.msnlabs.com or call 1-855-668-2369.

This Patient Information has been approved by the U.S. Food and Drug Administration.

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conception in humans. In humans, nephrogenesis is thought to be complete around birth; however, maturation of other aspects of kidney function (such as glomerular filtration and tubular function) may continue until approximately 2 years of age. It is unknown whether post-natal use of valsartan before maturation of renal function is complete has long-term deleterious effects on the kidney.

8.5 Geriatric Use

There were 4,143 heart failure patients 65 years of age and older in PARADIGM-HF *[see Clinical Studies (14)]*. Of the total number of sacubitril and valsartan-treated patients, 2,087 (49.6%) were 65 years of age and older, while 786 (18.7%) were 75 years of age and older in PARADIGM-HF. No overall differences in safety or effectiveness of sacubitril and valsartan have been observed between patients 65 years of age and older and younger adult patients.

No relevant pharmacokinetic differences have been observed in elderly (≥ 65 years) or very elderly (≥ 75 years) patients compared to the overall population *[see Clinical Pharmacology (12.3)]*.

8.6 Hepatic Impairment

No dose adjustment is required when administering sacubitril and valsartan to patients with mild hepatic impairment (Child-Pugh A classification). Half of the starting dose is recommended in adult and pediatric patients with heart failure and with moderate hepatic impairment (Child-Pugh B classification). The use of sacubitril and valsartan in patients with severe hepatic impairment (Child-Pugh C classification) is not recommended, as no studies have been conducted in these patients *[see Dosage and Administration (2.8) and Clinical Pharmacology (12.3)]*.

8.7 Renal Impairment

No dose adjustment is required in patients with mild (eGFR 60 to 90 mL/min/1.73 m^2) to moderate (eGFR 30 to 60 mL/min/1.73 m^2) renal impairment. Half of the starting dose is recommended in adult and pediatric patients with heart failure and with severe renal impairment (eGFR less than 30 mL/min/1.73 m^2). *[see Dosage and Administration (2.7), Warnings and Precautions (5.4) and Clinical Pharmacology (12.3)]*.

10 OVERDOSAGE

Limited data are available with regard to overdosage in human subjects with sacubitril and valsartan. In healthy volunteers, a single dose of sacubitril and valsartan 583 mg sacubitril/617 mg valsartan, and multiple doses of 437 mg sacubitril/463 mg valsartan (14 days) have been studied and were well tolerated.

Hypotension is the most likely result of overdosage due to the blood pressure lowering effects of sacubitril and valsartan. Symptomatic treatment should be provided.

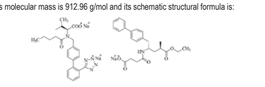
Sacubitril and valsartan is unlikely to be removed by hemodialysis because of high protein binding.

11 DESCRIPTION

Sacubitril and valsartan tablet is a combination of a neprilysin inhibitor and an angiotensin II receptor blocker.

Sacubitril and valsartan tablets contains anionic forms of sacubitril and valsartan, and sodium cations in the molar ratio of 1:1:3, respectively. Following oral administration, the drug substance dissociates into sacubitril (which is further metabolized to LBQ657) and valsartan. The drug substance is chemically described as Tri sodium (4-[([1S, 3R)-1-[1,1 '-biphenyl]-4-ylmethyl)-4-ethoxy-3-methyl-4-oxobutyl]amino]-4-oxobutanoate-(N-pentanoyl-N-[[2'-(1H-tetrazol-1-id-5-yl) [1,1'-biphenyl]-4-yl]methyl]-L-valinate).

Its molecular formula is $C_{48}H_{49}N_6O_9Na_3$. Its molecular mass is 912.96 g/mol and its schematic structural formula is:



Sacubitril and valsartan tablets are available as film-coated tablets for oral administration, containing 24 mg of sacubitril and 26 mg of valsartan; 49 mg of sacubitril and 51 mg of valsartan; and 97 mg of sacubitril and 103 mg of valsartan. The tablet inactive ingredients are colloidal silicon dioxide, crospovidone, croscarmellose sodium, magnesium stearate, microcrystalline cellulose and talc. The film-coat inactive ingredients are hypromellose, titanium dioxide, macrogol, talc and iron oxide red. The film-coat for the 24 mg of sacubitril and 26 mg of valsartan tablet and 97 mg of sacubitril and 103 mg of valsartan tablet also contains iron oxide black. The film-coat for the 49 mg of sacubitril and 51 mg of valsartan tablet also contains iron oxide yellow.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Sacubitril and valsartan contains a neprilysin inhibitor, sacubitril, and an angiotensin receptor blocker, valsartan. Sacubitril and valsartan inhibits neprilysin (neutral endopeptidase; NEP) via LBQ657, the active metabolite of the prodrug sacubitril, and blocks the angiotensin II type-1 (AT_1) receptor via valsartan. The cardiovascular and renal effects of sacubitril and valsartan in heart failure patients are attributed to the increased levels of peptides that are degraded by neprilysin, such as natriuretic peptides, by LBQ657, and the simultaneous inhibition of the effects of angiotensin II by valsartan. Valsartan inhibits the effects of angiotensin II by selectively blocking the AT_1 receptor, and also inhibits angiotensin II-dependent aldosterone release.

12.2 Pharmacodynamics

The pharmacodynamic effects of sacubitril and valsartan were evaluated after single and multiple dose administrations in healthy subjects and in patients with heart failure, and are consistent with simultaneous neprilysin inhibition and renin-angiotensin system blockade.

In a 7-day valsartan-controlled study in patients with reduced ejection fraction (HFrEF), administration of sacubitril and valsartan resulted in a significant non-sustained increase in natriuresis, increased urine cGMP, and decreased plasma MR-proANP and NT-proBNP compared to valsartan.

In a 21-day study in HFrEF patients, sacubitril and valsartan significantly increased urine ANP and cGMP and plasma cGMP, and decreased plasma NT-proBNP, aldosterone and endothelin-1. Sacubitril and valsartan also blocked the AT_1-receptor as evidenced by increased plasma renin activity and plasma renin concentrations. In PARADIGM-HF, sacubitril and valsartan decreased plasma NT-proBNP (not a neprilysin substrate) and increased plasma BNP (a neprilysin substrate) and urine cGMP compared with enalapril.

In PANORAMA-HF, a reduction in NT-proBNP was observed at Weeks 4 and 12 for sacubitril and valsartan (40% and 50%) compared to baseline. The NT-proBNP levels continued to decrease over the duration of the study with a reduction of 65% for sacubitril and valsartan at Week 52 compared to baseline.

QT Prolongation: In a thorough QTc clinical study in healthy male subjects, single doses of sacubitril and valsartan 194 mg sacubitril/206 mg valsartan and 583 mg sacubitril/617 mg valsartan had no effect on cardiac repolarization.

Amyloid-β: Neprilysin is one of multiple enzymes involved in the clearance of amyloid-β (Aβ) from the brain and cerebrospinal fluid (CSF). Administration of sacubitril and valsartan 194 mg sacubitril/206 mg valsartan once-daily for 2 weeks to healthy subjects was associated with an increase in CSF $Aβ_{1-38}$ compared to placebo; there were no changes in concentrations of CSF $Aβ_{1-40}$ or CSF $Aβ_{1-42}$. The clinical relevance of this finding is unknown *[see Nonclinical Toxicology (13)]*.

Blood Pressure: Addition of a 50 mg single dose of sildenafil to sacubitril and valsartan at steady state (194 mg sacubitril/206 mg valsartan once daily for 5 days) in patients with hypertension was associated with additional blood pressure (BP) reduction (approximately 5/4 mmHg, systolic/diastolic BP) compared to administration of sacubitril and valsartan alone.

Co-administration of sacubitril and valsartan did not significantly alter the BP effect of intravenous nitroglycerin.

12.3 Pharmacokinetics

Absorption

Following oral administration, sacubitril and valsartan dissociates into sacubitril and valsartan. Sacubitril is further metabolized to LBQ657. The peak plasma concentrations of sacubitril, LBQ657, and valsartan are reached in 0.5 hours, 2 hours, and 1.5 hours, respectively. The oral absolute bioavailability of sacubitril is estimated to be greater than or equal to 60%. The valsartan in sacubitril and valsartan is more bioavailable than the valsartan in other marketed tablet formulations; 26 mg, 51 mg, and 103 mg of valsartan in sacubitril and valsartan is equivalent to 40 mg, 80 mg, and 160 mg of valsartan in other marketed tablet formulations, respectively.

Following twice-daily dosing of sacubitril and valsartan, steady-state levels of sacubitril, LBQ657, and valsartan are reached in 3 days. At steady state, sacubitril and valsartan do not accumulate significantly, whereas LBQ657 accumulates by 1.6-fold. Sacubitril and valsartan administration with food has no clinically significant effect on the systemic exposures of sacubitril, LBQ657, or valsartan. Although there is a decrease in exposure to valsartan when sacubitril and valsartan is administered with food, this decrease is not accompanied by a clinically significant reduction in the therapeutic effect. Sacubitril and valsartan can therefore be administered with or without food.

Distribution

Sacubitril, LBQ657 and valsartan are highly bound to plasma proteins (94% to 97%). Based on the comparison of plasma and CSF exposures, LBQ657 crosses the blood brain barrier to a limited extent (0.28%). The average apparent volumes of distribution of valsartan and sacubitril are 75 and 103 L, respectively.

Metabolism

Sacubitril is readily converted to LBQ657 by esterases; LBQ657 is not further metabolized to a significant extent. Valsartan is minimally metabolized; only about 20% of the dose is recovered as metabolites. A hydroxyl metabolite has been identified in plasma at low concentrations (less than 10%).

Elimination

Following oral administration, 52% to 68% of sacubitril (primarily as LBQ657) and approximately 13% of valsartan and its metabolites are excreted in urine; 37% to 48% of sacubitril (primarily as LBQ657), and 86% of valsartan and its metabolites are excreted in feces. Sacubitril, LBQ657, and valsartan are eliminated from plasma with a mean elimination half-life ($T_{1/2}$) of approximately 1.4 hours, 11.5 hours, and 9.9 hours, respectively.

Linearity/Nonlinearity

The pharmacokinetics of sacubitril, LBQ657, and valsartan were linear over an sacubitril and valsartan dose range of 24 mg sacubitril/26 mg valsartan to 194 mg sacubitril/206 mg valsartan.

Drug Interactions:

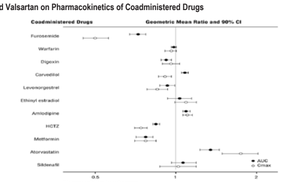
Effect of Co-administered Drugs on Sacubitril and Valsartan:

Because CYP450 enzyme-mediated metabolism of sacubitril and valsartan is minimal, coadministration with drugs that impact CYP450 enzymes is not expected to affect the pharmacokinetics of sacubitril and valsartan. Dedicated drug interaction studies demonstrated that coadministration of furosemide, warfarin, digoxin, carvedilol, a combination of levonorgestrel/ethinyl estradiol, amlodipine, omeprazole, hydrochlorothiazide (HCTZ), metformin, atorvastatin, and sildenafil, did not alter the systemic exposure to sacubitril, LBQ657 or valsartan.

Effect of Sacubitril and Valsartan on Co-administered Drugs:

In vitro data indicate that sacubitril inhibits OATP1B1 and OATP1B3 transporters. The effects of sacubitril and valsartan on the pharmacokinetics of coadministered drugs are summarized in Figure 1.

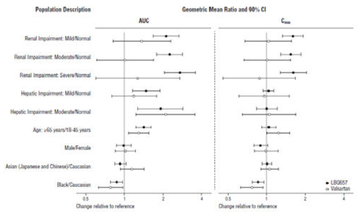
Figure 1: Effect of Sacub tril and Valsartan on Pharmacokinetics of Coadministered Drugs



Specific Populations

Effect of specific populations on the pharmacokinetics of LBQ657 and valsartan are shown in Figure 2.

Figure 2: Pharmacokinetics of Sacub tril and Valsartan in Specific Populations



Note: Child-Pugh Classification was used for hepatic impairment.

Pediatric Patients:

The pharmacokinetics of sacubitril and valsartan were evaluated in pediatric heart failure patients 1 to less than 18 years old administered oral doses of 0.8 mg/kg and 3.1 mg/kg of sacubitril and valsartan. Pharmacokinetic data indicated that exposure to sacubitril and valsartan in pediatric and adult patients is similar.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis and Mutagenesis

Carcinogenicity studies conducted in mice and rats with sacubitril and valsartan did not identify any carcinogenic potential for sacubitril and valsartan. The LBQ657 C_{max} at the high dose (HD) of 1200 mg/kg/day in male and female mice was, respectively, 14 and 16 times that in humans at the MRHD. The LBQ657 C_{max} in male and female rats at the HD of 400 mg/kg/day was, respectively, 1.7 and 3.5 times that at the MRHD. The doses of valsartan studied (high dose of 160 and 200 mg/kg/day in mice and rats, respectively) were about 4 and 10 times, respectively, the MRHD on a mg/m^2 basis.

Mutagenicity and clastogenicity studies conducted with sacubitril and valsartan, sacubitril, and valsartan did not reveal any effects at either the gene or chromosome level.

Impairment of Fertility

Sacubitril and valsartan did not show any effects on fertility in rats up to a dose of 73 mg sacubitril/77 mg valsartan/kg/day (≤1.0-fold and ≤0.18-fold the MRHD on the basis of the AUCs of valsartan and LBQ657, respectively).

13.2 Animal Toxicology and/or Pharmacology

The effects of sacubitril and valsartan on amyloid-β concentrations in CSF and brain tissue were assessed in young (2 to 4 years old) cynomolgus monkeys treated with sacubitril and valsartan (24 mg sacubitril/26 mg valsartan/kg/day) for 2 weeks. In this study, sacubitril and valsartan affected CSF Aβ clearance, increasing CSF Aβ 1-40, 1-42, and 1-38 levels in CSF; there was no corresponding increase in Aβ levels in the brain. In addition, in a toxicology study in cynomolgus monkeys treated with sacubitril and valsartan at 146 mg sacubitril/154 mg valsartan/kg/day for 39-weeks, there was no amyloid-β accumulation in the brain.

14 CLINICAL STUDIES

Dosing in clinical trials was based on the total amount of both components of sacubitril and valsartan, i.e., 24/26 mg, 49/51 mg, and 97/103 mg were referred to as 50 mg, 100 mg, and 200 mg, respectively.

14.1 Adult Heart Failure

PARADIGM-HF

PARADIGM-HF was a multinational, randomized, double-blind trial comparing sacubitril and valsartan and enalapril in 8,442 adult patients with symptomatic chronic heart failure (NYHA class II-IV) and systolic dysfunction (left ventricular ejection fraction ≤ 40%). Patients had to have been on an ACE inhibitor or ARB for at least four weeks and on maximally tolerated doses of beta-blockers. Patients with a systolic blood pressure of less than 100 mmHg at screening were excluded.

The primary objective of PARADIGM-HF was to determine whether sacubitril and valsartan, a combination of sacubitril and an RAS inhibitor (valsartan), was superior to an RAS inhibitor (enalapril) alone in reducing the risk of the combined endpoint of cardiovascular (CV) death or hospitalization for heart failure (HF).

After discontinuing their existing ACE inhibitor or ARB therapy, patients entered sequential single-blind run-in periods during which they received enalapril 10 mg twice-daily, followed by sacubitril and valsartan 100 mg twice-daily, increasing to 200 mg twice daily. Patients who successfully completed the sequential run-in periods were randomized to receive either sacubitril and valsartan 200 mg (N = 4,209) twice-daily or enalapril 10 mg (N = 4,233) twice-daily. The primary endpoint was the first event in the composite of CV death or hospitalization for HF. The median follow-up duration was 27 months and patients were treated for up to 4.3 years.

The population was 66% Caucasian, 18% Asian, and 5% Black; the mean age was 64 years and 78% were male. At randomization, 70% of patients were NYHA Class II, 24% were NYHA Class III, and 0.7% were NYHA Class IV. The mean left ventricular ejection fraction was 29%. The underlying cause of heart failure was coronary artery disease in 60% of patients; 71% had a history of hypertension, 43% had a history of myocardial infarction, 37% had an eGFR less than 60 mL/min/1.73m^2, and 35% had diabetes mellitus. Most patients were taking beta-blockers (94%), mineralocorticoid antagonists (58%), and diuretics (82%). Few patients had an implantable cardioverter-defibrillator (ICD) or cardiac resynchronization therapy-defibrillator (CRT-D) (15%).

PARADIGM-HF demonstrated that sacubitril and valsartan, a combination of sacubitril and an RAS inhibitor (valsartan), was superior to a RAS inhibitor (enalapril), in reducing the risk of the combined endpoint of cardiovascular death or hospitalization for heart failure, based on a time-to-event analysis (hazard ratio [HR] 0.80; 95% confidence interval [CI], 0.73, 0.87, p <0.0001). The treatment effect reflected a reduction in both cardiovascular death and heart failure hospitalization; see Table 4 and Figure 3. Sudden death accounted for 45% of cardiovascular deaths, followed by pump failure, which accounted for 26%.

Sacubitril and valsartan also improved overall survival (HR 0.84; 95% CI [0.76, 0.93], p = 0.0009) (Table 4). This finding was driven entirely by a lower incidence of cardiovascular mortality on sacubitril and valsartan.

Table 4: Treatment Effect for the Primary Composite Endpoint, Its Components, and All-cause Mortality in PARADIGM-HF

	Sacubitril and Valsartan N = 4,187 n (%)	Enalapril N = 4,212 n (%)	Hazard Ratio (95% CI)	*p*-value
Primary composite endpoint of cardiovascular death or heart failure hospitalization	914 (21.8)	1,117 (26.5)	0.80 (0.73, 0.87)	<0.0001
Cardiovascular death as first event	377 (9.0)	459 (10.9)		
Heart failure hospitalization as first event	537 (12.8)	658 (15.6)		
Number of patients with events:*	558 (13.3)	693 (16.5)	0.80 (0.71, 0.89)	
Cardiovascular death**	537 (12.8)	658 (15.6)	0.79 (0.71, 0.89)	
Heart failure hospitalizations				
All-cause mortality	711 (17.0)	835 (19.8)	0.84 (0.76, 0.93)	0.0009

*Analyses of the components of the primary composite endpoint were not prospectively planned to be adjusted for multiplicity.

**Includes patients who had heart failure hospitalization prior to death.

The Kaplan-Meier curves presented below (Figure 3) show time to first occurrence of the primary composite endpoint (3A), and time to occurrence of cardiovascular death at any time (3B) and first heart failure hospitalization (3C).

Figure 3: Kaplan-Meier Curves for the Primary Composite Endpoint (A), Cardiovascular Death (B), and Heart Failure Hospitalization (C)

Figure A

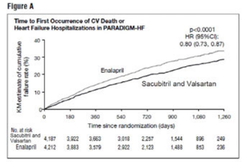


Figure B

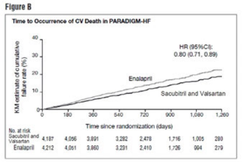
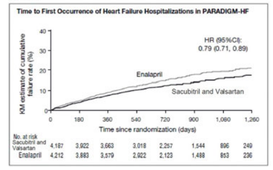
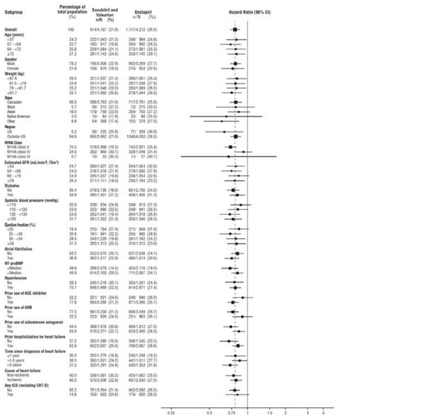


Figure C



A wide range of demographic characteristics, baseline disease characteristics, and baseline concomitant medications were examined for their influence on outcomes. The results of the primary composite endpoint were consistent across the subgroups examined (Figure 4).

Figure 4: Primary Composite Endpoint (CV Death or HF Hospitalization) - Subgroup Analysis (PARADIGM-HF)



Note: The figure above presents effects in various subgroups, all of which are baseline characteristics. The 95% confidence limits that are shown do not take into account the number of comparisons made, and may not reflect the effect of a particular factor after adjustment for all other factors. Apparent homogeneity or heterogeneity among groups should not be over-interpreted.

14.2 Pediatric Heart Failure

The efficacy of sacubitril and valsartan was evaluated in a multinational, randomized, double-blind trial PANORAMA-HF comparing sacubitril and valsartan (n = 187) and enalapril (n = 188) in pediatric patients aged 1 month to less than 18 years old due to systemic left ventricular systolic dysfunction (LVEF ≤ 45% or fractional shortening ≤ 22.5%). Patients with systemic right ventricle, single ventricle, restrictive cardiomyopathy or hypertrophic cardiomyopathy were excluded from the trial. Efficacy of sacubitril and valsartan in patients less than 1 year old was not established. At Week 52, there were 144 sacubitril and valsartan and 133 enalapril patients with a post-baseline assessment of NT-proBNP. The estimated least squares mean percent reduction from baseline in NT-proBNP was 65% and 62% in the sacubitril and valsartan and enalapril groups, respectively. While the between-group difference was not nominally statistically significant, the reductions for sacubitril and valsartan and enalapril were larger than what was seen in adults; these reductions did not appear to be attributable to post-baseline changes in background therapy. Because sacubitril and valsartan improved outcomes and reduced NT-proBNP in adults in PARADIGM-HF, the effect on NTproBNP was the basis to infer improved cardiovascular outcomes in pediatric patients.

16 HOW SUPPLIED/STORAGE AND HANDLING

Sacubitril/valsartan tablets are available as unscored, oval shaped, biconvex, film-coated tablets, containing 24 mg of sacubitril and 26 mg of valsartan; 49 mg of sacubitril and 51 mg of valsartan; and 97 mg of sacubitril and 103 mg of valsartan. All strengths are packaged in bottles as described below.

Tablet	Color	Debossment	NDC # 69539-XXX-XX	
Sacubitril/Valsartan		"M" and	Bottle of 60	Bottle of 180
24 mg/26 mg	Purple	S1	166-60	166-18
49 mg/51 mg	Light yellow	S2	167-60	167-18
97 mg/103 mg	Light pink	S3	168-60	168-18

Store at 25°C (77°F), excursions permitted between 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature]. Protect from moisture.

17 PATIENT COUNSELING INFORMATION

Advise patients to read the FDA-approved patient labeling (Patient Information).

Pregnancy: Advise female patients of childbearing age about the consequences of exposure to sacubitril and valsartan tablets during pregnancy. Discuss treatment options with women planning to become pregnant. Ask patients to report pregnancies to their physicians as soon as possible *[see Warnings and Precautions (5.1) and Use in Specific Populations (8.1)]*.

Lactation: Advise patients that breastfeeding is not recommended during treatment with sacubitril and valsartan tablets *[see Use in Specific Populations (8.2)]*.

Angioedema: Advise patients to discontinue use of their previous ACE inhibitor or ARB. Advise patients to allow a 36 hour wash-out period if switching from or to an ACE inhibitor *[see Contraindications (4) and Warnings and Precautions (5.2)]*.

Manufactured by:
MSN Laboratories Private Limited
Telangana – 509 228,
INDIA

Distributed by:
MSN Pharmaceuticals Inc.
Piscataway, NJ 08854 -3714

Issued on: 07/2024

DXXXXXX-XX

Exhibit B

FDA U.S. FOOD & DRUG ADMINISTRATION

ANDA 213748

ANDA APPROVAL

MSN Pharmaceuticals Inc.
U.S. Agent for MSN Laboratories Private Limited
20 Duke Road
Piscataway, NJ 08854-3714
Attention: Kondal Reddy Bairy
Vice President

Dear Kondal Reddy Bairy:

This letter is in reference to your abbreviated new drug application (ANDA) received for review on July 8, 2019, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) for Sacubitril and Valsartan Tablets, 24 mg/26 mg, 49 mg /51 mg, and 97 mg/103 mg.

Reference is also made to the complete response letter issued by this office on March 22, 2024, and to any amendments thereafter.

We have completed the review of this ANDA and have concluded that adequate information has been presented to demonstrate that the drug meets the requirements for approval under the FD&C Act. Accordingly, the ANDA is **approved**, effective on the date of this letter. We have determined your Sacubitril and Valsartan Tablets, 24 mg/26 mg, 49 mg /51 mg, and 97 mg/103 mg to be bioequivalent and therapeutically equivalent to the reference listed drug (RLD), Entresto Tablets, 24 mg/26 mg, 49 mg /51 mg, and 97 mg/103 mg, of Novartis Pharmaceuticals Corporation (Novartis).

The RLD upon which you have based your ANDA, Novartis's Entresto Tablets, 24 mg/26 mg, 49 mg /51 mg, and 97 mg/103 mg, is subject to periods of patent protection. The following patents and expiration dates are currently listed in the Agency's publication titled *Approved Drug Products with Therapeutic Equivalence Evaluations* (the "Orange Book"):

U.S. Patent Number	Expiration Date
8,101,659 (the '659 patent)	July 15, 2025*
8,877,938 (the '938 patent)	November 27, 2027*
9,388,134 (the '134 patent)	May 8, 2027*

9,517,226 (the '226 patent)	August 22, 2033
9,937,143 (the '143 patent)	August 22, 2033
11,058,667 (the '667 patent)	May 9, 2036
11,135,192 (the '192 patent)	August 22, 2033

* with pediatric exclusivity added

Your ANDA contains paragraph IV certifications to the '659, '938 and '134 patents, under section 505(j)(2)(A)(vii)(IV) of the FD&C Act stating that the patents are invalid, unenforceable, or will not be infringed by your manufacture, use, or sale of Sacubitril and Valsartan Tablets, 24 mg/26 mg, 49 mg /51 mg, and 97 mg/103 mg, under this ANDA. You have notified the Agency that MSN Laboratories Private Limited (MSN) complied with the requirements of section 505(j)(2)(B) of the FD&C Act. Litigation was initiated within the statutory 45-day period against MSN for infringement of the '659, '938 and '134 patents in the United States District Court for the District of Delaware [Novartis Pharmaceuticals Corporation v. MSN Pharmaceuticals Inc., et al., Civil Action No. 19-02053]. The 8 year period identified in section 505(j)(5)(B)(iii) of the FD&C Act, during which FDA was precluded from approving your ANDA, has expired.

With respect to the '226, '143, '667 and '192 patents, your ANDA contains statements under section 505(j)(2)(A)(viii) of the FD&C Act that these are method-of-use patents that do not claim any indication or other conditions of use for which you are seeking approval under your ANDA.

With respect to 180-day generic drug exclusivity, we note that MSN was a first ANDA applicant for Sacubitril and Valsartan Tablets, 24 mg/26 mg, 49 mg/51 mg, and 97 mg/103 mg, to submit a substantially complete ANDA with a paragraph IV certification. Therefore, with this approval, MSN may be eligible for 180 days of generic drug exclusivity for Sacubitril and Valsartan Tablets, 24 mg/26 mg, 49 mg/51 mg, and 97 mg/103 mg. This exclusivity, which is provided for under 505(j)(5)(B)(iv) of the FD&C Act, would begin to run from the date of the commercial marketing identified in section 505(j)(5)(B)(iv). The Agency notes that MSN failed to obtain tentative approval of this ANDA within 30 months after the date of which the ANDA was filed. See section 505(j)(5)(D)(i)(IV) of the FD&C Act (forfeiture of exclusivity for failure to obtain tentative approval). The Agency is not, however, making a formal determination at this time of MSN's eligibility for 180-day generic drug exclusivity. We will do so only if a subsequent paragraph IV applicant becomes eligible for full approval (a) within 180 days after MSN begins commercial marketing of Sacubitril and Valsartan Tablets, 24 mg/26 mg, 49 mg/51 mg, and 97 mg/103 mg, or (b) at any time prior to the expiration of the '659, '938, and '134 patents if MSN has not begun commercial marketing. Please submit correspondence to this ANDA notifying the Agency within 30 days of the date of the first commercial marketing of this drug product or the RLD. If you do not notify the Agency within 30 days, the date of first commercial marketing will be deemed

to be the date of the drug product's approval. See 21 CFR 314.107(c)(2).

Please note that if FDA requires a Risk Evaluation and Mitigation Strategy (REMS) for a listed drug, an ANDA referencing that listed drug also will be required to have a REMS. See section 505-1(i) of the FD&C Act.

COMPENDIAL STANDARDS

A drug with a name recognized in the official United States Pharmacopeia or official National Formulary (USP-NF) generally must comply with the compendial standard for strength, quality, and purity, unless the difference in strength, quality, or purity is plainly stated on its label (see FD&C Act § 501(b), 21 USC 351(b)). FDA typically cannot share application-specific information contained in submitted regulatory filings with third parties, which includes USP-NF. To help ensure that a drug continues to comply with compendial standards, application holders may work directly with USP-NF to revise official USP monographs. More information on the USP-NF is available on USP's website as https://www.uspnf.com/.

REQUIREMENTS AND RECOMMENDATIONS POST APPROVAL

Under applicable statutes, regulations, and guidances, your ANDA may be subject to certain requirements and recommendations post approval, including requirements regarding changes to approved ANDAs, postmarketing reporting, promotional materials, and annual facility fees, among others. For information on post-approval requirements and recommendations for ANDAs and a list of resources for ANDA holders, we refer you to https://www.fda.gov/drugs/abbreviated-new-drug-application-anda/requirements-and-resources-approved-andas.

Sincerely yours,

{See appended electronic signature page}

For Edward M. Sherwood
Director
Office of Regulatory Operations
Office of Generic Drugs
Center for Drug Evaluation and Research

Sarah Kurtz

Digitally signed by Sarah Kurtz
Date: 7/24/2024 11:11:06AM
GUID: 54078879000a1b9e15dd31ed6f0343ca

Exhibit C

UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF COLUMBIA

VANDA PHARMACEUTICALS, INC., Plaintiff, vs.	)	Civil Action No. 23-CV-280
UNITED STATES FOOD AND DRUG ADMINISTRATION, et al. Defendant,	)	March 6, 2023 12:42 a.m. Washington, D.C.
TEVA PHARMACEUTICALS, USA, INC. Intervenor Defendant.	)	

TRANSCRIPT OF MOTION FOR PRELIMINARY INJUNCTION

BEFORE THE HONORABLE TANYA S. CHUTKAN,

UNITED STATES DISTRICT COURT JUDGE

APPEARANCES:

FOR VANDA PHARMACEUTICALS:

PAUL WHITFIELD HUGHES , III
McDermott Will & Emery LLP
500 North Capitol St, NW
Washington, DC 20005
(202) 756-8981
Email: phughes@mwe.com

FOR U.S. FOOD and DRUG ADMINISTRATION:

ISAAC BELFER
U.S. Department of Justice
P.O. Box 386
Washington, DC 20044-0386
(202) 305-7134
Email: isaac.c.belfer@usdoj.gov

(APPEARANCES CONTINUED)

APPEARANCES (Continued):

FOR TEVA PHARMACEUTICALS:

BRIAN T. BURGESS
Goodwin Procter LLP
1900 N St NW
Washington, DC 20036
(202) 346-4000
Email: bburgess@goodwinlaw.com

Court Reporter:

Elizabeth Saint-Loth, RPR, FCRR
Official Court Reporter
U.S. Courthouse
Washington, D.C. 20001

This hearing was held via videoconference and is, therefore, subject to the limitations associated with sound/audio quality while using technology, i.e., slow connection, static interference, overlapping speakers, etc.

Proceedings reported by machine shorthand.
Transcript produced by computer-aided transcription.

P R O C E E D I N G S

THE COURTROOM DEPUTY: Your Honor, this is Civil Action 23-280, Vanda Pharmaceuticals, Incorporated versus Food and Drug Administration, et al.

Would the parties on this videoconference line identify yourselves for the record. We'll start with plaintiff's counsel this afternoon.

MR. HUGHES: Good afternoon, Your Honor. Paul Hughes of McDermott Will & Emery, for plaintiff Vanda Pharmaceuticals.

THE COURT: Good afternoon.

MR. BELFER: Good afternoon, Your Honor. Isaac Belfer, Department of Justice, for the government.

THE COURT: Good afternoon.

MR. BURGESS: Good afternoon, Your Honor. Brian Burgess from Goodwin Procter, for defendant intervenor, Teva Pharmaceuticals.

THE COURT: All right. Good afternoon, everyone. Thank you for accommodating me. I am in the middle of picking a jury, actually, so this is the only time we can do this today.

So the purpose of today's hearing is to resolve the pending motion for preliminary injunction in 23-cv-280, this case. I have reviewed the parties' briefs including their attachments, as well as the relevant statutes and case

law. I am going to give each party about ten minutes of oral argument. I have a couple of questions, but not many. And then I will -- it's my intention to rule on the motion.

But let me just briefly review some of the relevant background. You can, obviously, note any objection to my characterization of the background during your argument.

A generic drug manufacturer may seek FDA approval through an abbreviated new drug application, or "ANDA," under 21 U.S.C. Section 355(j). ANDAs do not attempt to prove that the proposed generic drug is safe or effective for its effective use -- for its intended use. Excuse me. Instead, in order to obtain marketing approval, an ANDA applicant need only show that a proposed generic drug is the same as the original listed drug.

What's relevant here, that sameness standard requires that the labeling proposed for the generic drug is the same as the labeling approved for the listed drug under 21 U.S.C. Section 355(j)(2)(A)(v).

There are two statutory exceptions in which the labeling can be different. One is when the changes are approved in advance by the FDA in response to a suitability petition; and two, when the changes in the labeling are required because the new drug and the listed drug are produced or distributed by different manufacturers. That's

21 U.S.C. Section 355(j)(2)(A)(v).

Relatedly, the "sameness" standard requires that the conditions of use prescribed, recommended, or suggested in the labeling proposed for the generic drug have been previously approved for the brand-name drug. Again, 21 U.S.C. Section 355(j)(2)(A)(i); 21 C.F.R. Section 314.94(a)(4)(i).

Now, broadly speaking, there appear to be three pathways for concerned parties to administratively challenge an ANDA. Those challenges can be lodged at different stages of the approval process.

The first is signing a petition with the FDA before it makes a final decision on approving a generic drug. That's under 21 U.S.C. Section 355(q). Once this kind of petition is pending, the statute bars judicial review of the underlying issues until it is resolved. I refer you to Section 355(q)(2)(B) which directs the Court to dismiss without prejudice for failure to exhaust any suit concerning the same issues in the petition until final action has been taken.

The second is by filing a request for the FDA to stay the effects of a final decision, within 30 days of the decision. And that's 21 C.F.R. Section 10.35(b).

And the third, the filing, at any time, of a general petition for an administrative proceeding asking FDA

to issue, amend, or revoke a regulation or order or to take or refrain from taking any other form of administrative action, 21 C.F.R. Section 10.25. The FDA must respond to such a petition within 180 days. And if this kind of petition is pending, an FDA regulation states that the petition must be resolved before a suit can be filed challenging the same action or nonaction that the petition challenges. 21 C.F.R. Section 10.45(b). If such a premature suit is filed, the regulation provides FDA shall request dismissal on the grounds of failure to exhaust, lack of final agency action, and lack of actual controversy.

As I will discuss, this case involves mainly the third type of administrative challenge. In 2014, FDA approved Hetlioz, H-E-T-L-I-O-Z -- I hope I am pronouncing that correctly. The brand name for that is tasimelteon drug -- T-A-S-I-M-E-L-T-E-O-N drug -- which is designed to treat Non-24-Hour Sleep-Wake Disorder, or "Non-24." Non-24 is a chronic disorder frequently affecting visually impaired people in which the body cannot synchronize its internal circadian clock with the 24-hour day.

While seeking initial FDA approval for Hetlioz, Vanda voluntarily proposed to repeal the Hetlioz proprietary name, and its approved strength in Braille -- excuse me -- Vanda voluntarily proposed to repeat -- excuse me -- the Hetlioz proprietary name, and its approved strength in

Braille on the label. FDA allowed Vanda to do so, but also asked Vanda to include on the label the statements, "Dispense in original container," and "Do not cover Braille."

In 2018, Teva submitted an ANDA seeking approval to market a generic version of tasimelteon. Teva's proposed label did not include Braille. The FDA nonetheless decided to approval the label, reasoning that: While Braille was nice to have, it had not been a condition of approval for the original listed drug, Hetlioz.

Relatedly, FDA also determined that Teva did not need to include the accompanying statements "Dispense in original container," and "Do not cover Braille."

FDA approved Teva's ANDA on December 12, 2022, and the label had no Braille or accompanying statements. Teva has since started selling and shipping its generic tasimelteon.

Vanda sought a copy of Teva's approval label under the Freedom of Information Act, and received it from FDA on December 23rd, 2022.

On January 25th, 2023, Vanda filed a petition with FDA asking it to revoke its approval of Teva's ANDA and order a re-call of Teva's product. This is the third type of administrative challenge I described, which is raised pursuant to 21 C.F.R. Section 10.25.

FDA informed Vanda that, per its regulations, it would respond within 180 days. Vanda had not previously filed a preapproval petition challenging the legality of Teva's ANDA, nor had it requested a stay on the FDA's approval within the 30-day window for that request.

Six days later, on January 31st, Vanda filed its complaint in this case alleging that FDA's approval of Teva's generic tasimelteon label violated the APA as arbitrary and capricious, and not in accordance with the law. Shortly thereafter, I granted Teva Pharmaceutical's motion to intervene as a defendant.

On February 8, Vanda moved for a preliminary injunction that would vacate or suspend FDA's approval of Teva's ANDA and compel FDA to order Teva to recall all of its tasimelteon. Vanda asserts that it cannot wait 180 days for FDA's decision on its petition, and needs relief immediately.

So I am going to hear from the parties now. We'll start with Vanda and then the defendants, and then I will give Vanda brief rebuttal. I want you to proceed with the assumption and understanding that I have read your brief and looked at the exhibits.

So counsel for Vanda.

MR. HUGHES: Thank you, Your Honor.

And just to begin with one small record correction

of what the Court recited. Vanda received the FOIA response on December 30th. December 23rd was the date that FDA sent us that CD, a physical CD.

THE COURT: I see.

MR. HUGHES: But it was received in my office on December 30th. So we have put in a declaration to the Court just to that effect, just that one point.

THE COURT: Thank you.

Just to clarify, did Vanda know at any point before Teva's label was approved that Teva's proposed label as part of its ANDA would not include Braille?

MR. HUGHES: No, Your Honor. Vanda did not.

And I do want to address one factual point that Teva raises. They have attached to their brief a piece of deposition transcript that came from a patent dispute between Teva and Vanda where that question was asked to a Teva official.

The important thing about that, Your Honor, is that that deposition transcript, as it says at the top of the page, was marked "highly confidential" and "prosecution bar" so, as a result of the protective order that was in place in that case, no one at Vanda had access to that material. No one at Vanda knew about that material. And, what's more, Vanda was not allowed to use that material for anything other than patent litigation. So the only people

who knew about that was Vanda's patent counsel at Paul Weiss who, pursuant to the protective order, was not at liberty to disclose that information to Vanda. So Vanda did not have information about the lack of Braille until December 30th when my office received the FOIA response that provided us, for the first time, Teva's label.

THE COURT: Okay. Go ahead.

MR. HUGHES: Your Honor, I think there would be two different places to begin, and I just want to start wherever it's most helpful for the Court.

I could begin with the same labeling requirement on the merits, or I could turn right to the 10.45(b) argument that the Court identified. And I would be happy to take direction from the Court as to where you would like me to --

THE COURT: If you could start with the latter.

MR. HUGHES: Thank you, Your Honor.

So turning to the 10.45(b) argument, Your Honor, I think there are a few reasons why that doesn't pose an exhaustion obstacle here. Again, this isn't a framework where FDA suggests that we should wait at least 180 days for a response.

As another court in the *Bracco* case said, the 180 days is often not a firm limit. FDA often says that 180 days will take some greater amount of time. But Section 704

of the Administrative Procedure Act very clearly delineates the scope of agency-created administrative exhaustion that can appropriately be a bar to judicial review of what is otherwise final agency action. We submit this is absolutely final agency action because it's the sole basis on which Teva is in the marketplace selling this product.

What 704 says is that it either has to be statutory-based exhaustion, which this is not, or it has to be a regulation from the agency that does two things: One, creates an internal administrative appeal; and two, renders inoperative the underlying order during that agency appeal. Neither of those two things appropriately describe what 10.45(b) does.

And so, as we pointed out in the reply brief, when several courts have looked at similar administrative structures, they found that those are simply not the kind of administrative exhaustion scheme that is a basis to bar this Court's review under the Administrative Procedure Act under 704. That's our first argument.

Our second argument, which is completely independent from that, is under the principles of *McCarthy v. Madigan* as FDA itself has admitted in other cases.

That rule is subject to exceptions of judicial discretion even if the Court thinks that that rule would otherwise apply. In their multiple reasons that even if the

Court were to think -- contrary to our principle submission that 10.45(b) applies -- that it should exercise discretion not to apply it here as multiple courts in this district have done.

The first is our demonstration that there would be irreparable harm both to the company -- the company's goodwill, as well as the real safety risk that results to patients. The second, though, which is related is the reasonableness of the 180-day time frame in the context of the nature of the claim that is being raised.

The nature of our claim that's being raised is there is safety information that was put on the label that we maintain the FDCA requires to be placed on a generic label as well, and that the failing to do so makes the product less safe. We think that's the kind of claim that can't wait half a year for resolution and is precisely what fits quite well within this.

The third basis for I think the Court applying its discretion here would be a notion that this has already been decided by FDA. FDA has pointed that out, that there was an internal agency decision.

FDA, in its briefing to this Court, has made quite clear what its position on the merits is. It says, for example, at page 23 of its brief -- this is a section heading: FDA's decision did not violate the same labeling

requirement. FDA has, I think, very clearly told us what its position on the merits here is, and we think that's a straightforward legal question that would be appropriate for this Court to resolve at this time. Because if we're right in our submission as to what the straightforward meaning of the legal framework is, that, we think, would resolve this case directly in Vanda's favor. And FDA has quite clearly asserted that we're incorrect about that. And so we submit that it's appropriate for the Court to resolve that core legal dispute at this juncture.

I am happy, Your Honor, to address any more points --

THE COURT: Well, we're here on a motion for preliminary injunction. You argue that Teva's labels without the Braille will harm Vanda because it would inevitably stain the goodwill of the tasimelteon market. But if patients experience problems because of Teva's labels, won't they blame that on Teva and not Vanda? In fact, wouldn't that make patients more likely to prefer Vanda?

MR. HUGHES: Well, Your Honor, what is happening in the marketplace is because of state automatic substitution laws. Patients are being switched without their consent and often without their foreknowledge from Vanda's Hetlioz product to Teva's generic that lacks

Braille. Our point is, this goes to the market of tasimelteon as a whole.

The risk that we see right now is: If a patient has an adverse health outcome, a doctor gave an overdose, or something along those lines, because they can't distinguish their medication in the way that they have been doing for years, that is going to be attributable to the tasimelteon market as a whole which directly affects Vanda's interest because Vanda is the one who created this market and it's created the goodwill of this market, being especially one that works for the interest of blind patients. That's why Vanda's won awards for its work in this area, and all the steps it's taken to make sure that this isn't, in fact, a highly accessible product.

Again, I think it's important to juxtapose; as the Court is aware, there is another generic ANDA application from MSN Pharmaceuticals, and MSN Pharmaceuticals included Braille on its label. So there is not some basis to suggest that Teva can't do this or lacks the ability to do this. Another generic manufacturer, in fact, has done this, and FDA has approved that action from the other generic.

And our point is the failure to do so creates safety risks which has a real risk for Vanda's goodwill and reputation in this marketplace with which it is absolutely inherently connected.

THE COURT: All right. Thanks.

I am not -- I am going to hold off on the merits at this junction. I will hear now from FDA, and then I will hear from Teva.

MR. HUGHES: Thank you, Your Honor.

MR. BELFER: Thank you, Your Honor.

So if it works for the Court, I would like to start with argument about why this lawsuit is incurably premature because that will then have significance for the ripeness and the exhaustion argument.

So under well-established precedent, when a party challenges an FDA action as filed in this citizen petition and then it files a lawsuit while that citizen petition is pending charging the same action, that lawsuit is incurably premature.

THE COURT: Well, hold on a second. Let me ask you.

Is Vanda right? -- maybe you are saying, no, they're not -- the exhaustion requirement is not triggered by agents to rule unless the rule also provides for the method of exhaustion to stay the effects of the agency decision that's being challenged?

MR. BELFER: So Vanda's reference is 5 U.S.C. 704. But 704 only applies where you have agency action that is otherwise final.

Here, what we have explained is that: FDA's

approval of Teva's ANDA is not final with regard to Vanda because Vanda has filed a citizen petition asking that we reconsider that decision. So under D.C. Circuit precedent, because Vanda filed the citizen petition asking FDA to reconsider its decision to approve Teva's ANDA, that renders an FDA decision nonfinal with regard to Vanda. So the provision of 704 that Vanda's counsel just described isn't applicable here.

THE COURT: What kind of input should I anticipate -- let me -- again, this is the last time I will interrupt you.

What kind of input do you anticipate FDA being able to give in resolving Vanda's petition that could affect this Court's resolution of the legal issues in this case?

MR. BELFER: So Vanda's citizen petition raises a number of arguments and presents variance evidence regarding whether the omission of Braille makes Teva's product less safe. And so there are a lot of new arguments and evidence regarding safety in Vanda's citizen petition, and those have an impact when FDA is applying the difference in the manufacturer exception of the same legal requirements.

One of the factors the FDA considers is whether a difference would make the product less safe. And so the factual issues regarding safety in Vanda's citizen petition are important for this case, and those have been presented

to FDA in a citizen petition; so for a variety of reasons, it's appropriate for this Court to give FDA an opportunity to resolve those factual questions regarding safety to consider them to apply FDA's scientific expertise to those questions, and to develop a record of those questions.

Additionally, that would further judicial economy because depending on how the FDA rules in the citizen petition it could obviate the need for this case on a whole; FDA could find for Vanda or FDA might alter the legal issues presented. Depending on how FDA rules on the citizen petition, that could affect the issues in this case or, at the very least, it would provide a further factual background that is helpful for this case. So for all of those reasons -- both because it's mandated by D.C. Circuit precedent and because -- for all of those, kind of, policy concerns and judicial economy concerns, we think it would be appropriate for this Court to allow FDA to resolve Vanda's citizen petition before deciding this case.

So just to close the loop on the incurably premature issue, I wanted to note a few points on that. The first is, under this Court's decision in the *King* case, courts do not tend to look at how a petition is framed, how it's styled; they look to the substance of the request. And here, the substance of Vanda's request is for reconsideration. Substantively, Vanda is asking FDA to

reconsider its decision to grant Teva's ANDA.

I would also direct the Court to the citizen petition itself. I think this is instructive. This is Exhibit 26; it's Vanda's citizen petition.

So, on page 2 of the citizen petition, Vanda asks FDA to use both its statutory and regulatory authority and its inherent authority to revoke the approval of Teva's ANDA. And then, on page 14 of Exhibit 26, Vanda is explaining why FDA has inherent authority to revoke Teva's ANDA. Vanda cites the *Mazaleski* case from the D.C. Circuit. It quotes that case, saying: We have many times held that an agency has the inherent power to reconsider and change a decision if it does so within a reasonable period of time.

So, in other words, Vanda is quoting the D.C. Circuit *Mozeleski* case for the proposition that agencies have the power, the inherent authority, to reconsider and change a decision. And so I think that shows that, in substance, what Vanda is seeking is reconsideration of FDA's decision to grant Teva's citizen petition. And because they have submitted a request for reconsideration and that remains pending, that renders FDA's approval of Teva's ANDA nonfinal as to Vanda, and renders this suit incurably premature. And so that has implications for our prematurity argument.

So regarding ripeness -- there are two factors for

ripeness: First, whether an issue is fit for judicial review; and second, whether the party would suffer immediate significant hardship from withholding judicial review.

With regard to the first factor, fitness for judicial review, courts have held that an issue is not fit for judicial review if the underlying decision is not final. If there is no final agency action, it is not fit for judicial review. For the reasons we just discussed, because Vanda had been pending citizen petition asking FDA to reconsider its decision to grant Teva's ANDA, that renders FDA's decision not final as to Vanda, making these issues not fit for judicial review.

Additionally, as we also discussed, there are many factual issues regarding safety of the Vanda citizen petition, and those factual issues benefit from further factual development. They benefit from FDA being able to consider those factual safety issues, apply expertise to those issues, and develop a factual record. So it would then benefit any future judicial decision. So, for those reasons, this case is not fit for judicial review.

And then, on the other factor, Vanda has not shown that it would suffer immediate and significant hardship that would be sufficient to outweigh the fact that this case is not fit for judicial review, and that goes to the irreparable harm argument as we discussed in our brief.

Vanda has not shown it would suffer irreparable harm; it hasn't met its burden to show that. So that is ripeness.

Our final argument relating to prematurity is exhaustion. And so this is 21 C.F.R. 10.45(b) which requires a joinder movant that before filing a suit challenging an FDA decision a party must file a citizen petition and get FDA's final decision on the citizen petition before bringing suit.

Now, Vanda argues for various exceptions to this requirement, but none of those exceptions to that requirement apply here.

First, as discussed earlier, there is no final agency action here because Vanda has a pending citizen petition asking FDA to reconsider its grant of Teva's ANDA that rendered FDA's decision to approve the ANDA nonfinal as to Vanda. So because there is no final agency action, the exception -- or the argument based on 5 U.S.C. 704 does not apply. As we discussed, 5 U.S.C. 704 -- that provision only applies if you have final agency action.

Vanda also argues that it will suffer irreparable harm, and so cannot wait for FDA to resolve this. But for the reasons discussed in our brief, Vanda has not met its burden of showing a clear showing of irreparable harm.

And it's also notable, as Your Honor noted, that Vanda had several opportunities to seek relief with FDA

earlier. It could have filed its petition under 355(q) while the ANDA was pending; which is a very common thing, by the way, for brand-new companies to do. It's very common for brand-new companies to file that kind of preemptive petition to try and lock in things that don't meet the safety requirement. So Vanda could have filed the civil petition while the ANDA was pending; it didn't do that. It also didn't file a request to stay. So, for all of those reasons, it hasn't shown any harm that would require -- that counsel in favor of excusing its failure to exhaust.

And it also argues, under safety concerns, here, with reportedly failure to exhaust, but that's not true. FDA is the agency that is entrusted by Congress -- it is entrusted by Congress to evaluate the safety of drugs.

FDA has the scientific expertise and the statutory authority to make safety determinations regarding whether a drug is safe to be on the market. And here FDA did not find that the lack of Braille on Teva's label caused a safety concern. To the contrary, it's implicit in FDA's finding that the different manufacturer exception (indiscernible) applies was a finding that the lack of Braille did not render Teva's label any less safe; and it ended up ultimately approving Teva's ANDA. FDA appropriately found that Teva's product was just as safe and effective as Hetlioz.

And it's also significant that -- people who are blind take many different drugs, many different medications, and none of those have Braille. So it's very standard for drugs that blind people take not to have Braille. The FDA has not found that any of those drugs pose a safety concern.

THE COURT: Okay. I didn't go into the merits with counsel for Vanda for reasons that I will explain.

I am not trying to cut you off, but I am trying to adhere to the time requirements only because I have a very limited amount of time for this. I am going to cut you off, and I'm sorry for that, unless there is some other -- unless you had some other argument that wasn't related to the merits.

MR. BELFER: So I think just relating to the exhaustion issue -- I apologize -- I want to make one final point which is that I think Vanda, in its statement, argued that -- exhaustion is not necessary because there is no need for FDA to make a further decision because FDA has already taken a position on this, it's already addressed safety. And my response to that is just that while it's true that FDA did address safety concerns in granting Teva's ANDA, FDA has not been presented with a particular safety argument, evidence, in Vanda's citizen petition. So because Vanda did present new argument, evidence regarding safety in its citizen petition, FDA should be given an opportunity to

address those.

THE COURT: All right. Counsel for Teva, briefly.

MR. BURGESS: Thank you, Your Honor.

I would like to start by addressing the exhaustion issue, and then I will address the other factors going to irreparable harm and the balance of interest.

On exhaustion, Vanda's position, in its argument based on 704 of the APA, runs directly contrary to numerous decisions in this circuit, including a decision from the D.C. Circuit on the issue.

As we noted in our brief and as the government noted in our brief, and in the *Association of American Physicians'* case, the court addressed, really, the exact same scenario, where a third party was seeking to challenge the approval of a drug after the fact, without having exhausted the administrative process. And the court held -- Judge Bates, within the district court, and the D.C. Circuit -- that that claim was not exhausted.

Vanda, in its reply brief, argued that, well, that was resolved as to lack of standing and wasn't injury there; but, in both decisions, the court clearly had alternative holdings, relying both on lack of standing and exhaustion. Vanda also suggested that maybe the Court was unaware of its argument based on 704 and didn't address it. But if you look at the briefing in both cases, the exact argument that

Vanda is pressing here was made to the Court, and it was rejected. Judge Bates, in his decision, explained why.

He said the *Darby* case about courts not being able to impose their own prudential exhaustion requirements, specifically except situations like this, provided for under the FDA regulation where there is a mandatory exhaustion requirement. So Vanda's position on that is just directly contrary to those decisions. It's also directly contrary to Chief Judge Howell's decision in the *Teva v. FDA* case that we also cited in our brief that Vanda didn't address in its reply brief.

So to allow a company to skip over the administrative process would represent a significant break with precedent; a significant break with how these issues have been adjudicated. We also think it's contrary to the intent indicated by Congress with a provision like 355 22.

I agree with Your Honor that that's not the exact type of petition that's at issue here. But if what Vanda is doing were allowed to succeed, it would create a dramatic loophole around what Congress is trying to address; which is it's premised on the idea that to challenge the approval of a drug, brands are expected to go through the administrative process, and the FDA is expected to have an opportunity to complete the administrative process before someone jump s ahead to Court.

So for Vanda to be able to bypass that and seek the exact same relief without having exhausted its administrative remedies, we think would mean serious tension unlike Congress expected, and would be contrary to numerous decisions in this court.

We also think there is no practical basis to excuse exhaustion here, even if that were possible. As Mr. Belfer indicated, it's very customary for brand companies to bring citizen petitions in anticipation of potential issues the FDA might have -- that might be presented.

So even accepting Vanda's representation that it was unaware of this issue because it was limited to outside counsel, it certainly could anticipate a novel argument it's making, is the first ever product approved with Braille, and it's making a novel argument about -- that the formatting of Braille, that it needs to be applied to the generic, we think that was contrary to existing FDA guidance. If Vanda had a contrary view, it certainly had notice that it could present that in an ordinary citizen petition process, rather than jumping to court after the fact and seeking injunctive relief.

Turning then, I guess, to the other factors regarding irreparable harm and the harm to Teva -- to Your Honor's question about the reputational injury that Vanda is

claiming, I think it's entirely too speculative. The case that they rely on for that point, *Atlas Air*, shows why. In that case, Judge Moss recognized that a harm to reputation could, in some instances, be irreparable, but it can't be supported just by conjecture. There the plaintiff actually came forward with the affidavit showing the customers -- because of the conduct at issue -- had been issuing complaints, that there had been genuine problems. There is nothing like that here. We just have Vanda's speculation about what it thinks is going to happen in the market, even though our product has been on the market for three months. There is no reason that it needs to rely on speculation about what would happen.

To Mr. Hughes' point about automatic substitution and the fact that products can be changed at the pharmacy level, there is every reason to think that patients are going to become aware if there is a change; their co-pay can change when being filled with a generic product rather than their brand.

As Vanda noted in its brief, there are different payment assistance programs that apply if you are getting a Vanda product versus a Teva product. So the speculation that there is going to be some harm, which we disagree with, and the further layer of speculation that that harm is going to be attributed to Vanda, we just don't think is supported

and can establish irreparable injury.

Vanda's other theories of irreparable injury really just go to the fact that they have to compete with a generic at all, which we think is really disconnected from the type of claim that it is asserting here; it's also just not supported by the record.

As we noted in our brief, public documents establish that Vanda has more than half a billion dollars in cash, cash equivalents, or marketable securities. So the notion that a couple of months litigating here and what Vanda itself, in discussing the potential bond that would be at issue estimates, it's a few million dollars a month -- the idea that that is going to cause irreparable injury to Vanda, we just don't think is supported and is contrary to the D.C. Circuit's strict case law about economic injury.

Adversely, Teva would be negatively impacted by a mandatory injunction that would disrupt the status quo substantially. We have done everything that FDA has asked us to do. We have invested in developing and commercializing this product. We have also invested in multiple rounds of litigation with Vanda, including prevailing in the patent litigation. That's exactly what the Hatch-Waxman Act envisions; the generics that make that investment are supposed to be able to come into the market. For Vanda to now come in after the fact without having

participated in the administrative process to try to disrupt our approval without serious consequences for Teva including, as we noted in our brief, it would interrupt and it would effectively take away our statutory exclusivity as one of the first ANDA filers to bring a paragraph forced implication [sic] on this product, which is an award of exclusivity that Congress recognized, incentivized. The kind of challenges that Teva brought, courts in this circuit have recognized that the loss of that statutory exclusivity would be irreparable harm, and repeatedly denied. Motions for preliminary injunction where the effect of granting the relief the plaintiff seeks would be to take away the statutory exclusivity the generic has.

The way exclusivity works, it starts from when we enter the market, and it can't stop. So if our approval were suspended or we were otherwise taken off the market the way Vanda is trying to attempt, we would just end up losing that exclusivity. So there is a significant harm to Teva.

We also think the public interest clearly favors denying the extraordinary relief that Vanda is seeking. This is a very expensive product. Vanda has been on the market for over eight years; it's the sole provider of the product. It costs $25,000 for a set of 30 pills. The cost savings that Teva is bringing, that generics would generally bring, are clearly in the public interest. Numerous

decisions in this court have recognized that. And Vanda's speculation about safety, which runs contrary to the judgment of the FDA and is based -- we don't think is supported, among other things.

As the FDA noted in its brief, only 10 percent of the blind population even reads Braille. So the notion that this is an imminent public safety issue, we don't think is supported. And public interest in lowering access to lower cost generic drugs as Congress intended clearly supports denying this extraordinary relief they're requesting.

THE COURT: Thank you.

Mr. Hughes, I am going to give you very brief rebuttal.

MR. HUGHES: Thank you, Your Honor. And I will be brief.

I would like to focus on the procedural issues and how if -- it seems that the defendants think this claim should be brought. They suggested this claim could be brought years ago just through something of an earlier-filed citizen petition. But we don't think that's a well-founded claim, Your Honor, because you have to have a basis to bring a citizen petition and Vanda had no inkling that Teva would not use Braille in its label.

Again, as we pointed out, another generic, MSN did so. And we had every reason to expect that Teva and FDA

would apply the law as written. So the suggestion that we should have filed a citizen petition years ago when we had no basis to think that this was a plausible issue, I don't think is well-founded.

So then what happens after we have this information? Well, Mr. Belfer's argument on administrative exhaustion suggests that the reason we haven't exhausted is because we have rendered the underlying agency action nonfinal through a citizen petition which he believes is, essentially, a reconsideration.

Now, I think that submission is wrong on the face of it because there is nothing that is nonfinal about this ANDA. Teva is in the marketplace selling solely because of its ANDA which has real practical effects, so it's absolutely final.

Let me just say, if there is a glimpse of any doubt, if the government's concern is that the existence of a citizen petition is what renders this case nonfinal, it means the Court shouldn't proceed to review; we'll just withdraw the citizen petition. As the D.C. Circuit said in *Columbia Falls*, if there is some sort of reconsideration issue before an agency that could provide any question or concern for the administrative exhaustion, a party can just remedy that by withdrawing.

Now, I am going to get that Mr. Belfer would not

think that that would put this case properly before the Court because I think he would say that we're in a box where we have to file the citizen petition, and FDA then has to get 180 days. So under that view of the world, there is no way for Vanda to be able to get judicial review anywhere within 180 days of us learning of this information at all. We don't think that is a possibly plausible submission.

And that's why, even if the Court disagrees with us on the 704 argument -- I will come back to that in a minute -- that's why what FDA itself has even admitted in the *American Association of Physicians* case to which Mr. Burgess pointed, even if you think that 10.45 is in some way applicable, which we don't, the Court still retains discretion to say: Exhaustion is not required under these circumstances because there will be cases in which a court has to be able to reach this issue faster than the 180-day box that FDA would want to erect.

We think this is exactly such a case for the safety issues that Dr. Stein -- the most senior official at FDA who looked at this issue -- he plainly articulated the safety risk of taking Braille that had been on this label for more than eight years, taking it off. And no one at FDA has responded to that clear safety concern that FDA itself advanced.

THE COURT: Okay.

MR. HUGHES: Thank you, Your Honor.

THE COURT: You said you had one other -- there was another point you wanted to make?

MR. HUGHES: We were just turning back to the 704 argument, Your Honor. We think we have fully articulated that in the briefs. It's absolutely a correct point.

But even setting that aside, we think that it's clear the Court has discretion not to require this 180-day waiting period. And it's not a box the FDA can erect to say that there is no judicial review over this action for 180 days. And the equities, as we have demonstrated, I think are quite clear. The safety concerns behind the enormous impact on Vanda, both with respect to its goodwill and to the exclusivity that it's now lacking through what we believe was an unlawful approval of ANDA.

At the end of the day, this is a straightforward legal question. And if we're right about the meaning of the law, I think it's correct to say that the preliminary injunction should be granted and that the ANDA should be suspended pending fulsome resolution on the merits.

THE COURT: All right. Thank you.

Give me one moment.

All right. A preliminary injunction is an extraordinary remedy never awarded as of right; *Winter v. Natural Resources Defense Council*, 555 U.S. 7, at 24. And, therefore, the party seeking it bears the burden of making a clear showing they are entitled to the relief they seek. Specifically, plaintiffs must clearly show, one, that they're likely to succeed on the merits; two, that they're likely to suffer irreparable harm in the absence of preliminary relief; three, that the balance of equities tips in their favor; and four, that an injunction is in the public interest. Those are well-established factors. I am quoting from *Sherley versus Sebelius*, 644 F.3d 388, at 392, which quoted *Winter*. The third and fourth factors merge when the government is the opposing party under *Nken v. Holder*, 556 U.S. 418, at 435.

Where, as here, a party seeks to change rather than preserve the status quo, and to command the U.S. government, the standard for granting a preliminary injunction is particularly high. And I cite *Kondapally v. U.S. Citizenship & Immigration Services*, 2020 Westlaw, 5061735, at *3.

However, before deciding to grant injunctive relief, I must first determine whether it's appropriate to

exercise jurisdiction over the case. I cite *Aamer v. Obama*, 742 F.3d 1023, at 1028. Here, too, plaintiff bears the burden of showing a likelihood of success. *Obama versus Klayman*, 800 F.3d 559, at 565.

Defendants raise three jurisdictional issues with this action: Administrative exhaustion, finality, and ripeness. At this preliminary stage, I am not inclined to dismiss the suit on any of those grounds; but I will briefly review some of the potential issues they raise.

With regard to exhaustion: No one is entitled to judicial relief for a supposed or threatened injury until the prescribed administrative remedy has been exhausted. *Association of Flight Attendants-CWA v. Chao*, 493 F.3d 155, at 158.

A case of the administrative exhaustion requirement ensures that agencies and not the federal courts take primary responsibility for implementing their regulatory programs assigned by Congress. Here, FDA regulation expressly requires exhaustion. A request that FDA take or refrain from taking any form of administrative action must first be the subject of a final administrative decision based on a petition before any legal action is filed in a court complaining of the action or failure to act. I am quoting from 21 C.F.R. Section 10.45(b).

If such a legal action is brought before the FDA

has resolved that petition, the regulation commands FDA to request dismissal of the court action or referral to the agency for an initial administrative determination on the grounds of a failure to exhaust administrative remedies, the lack of final agency action as required by 5 U.S.C. Section 701, *et seq.*, and the lack of an actual controversy as required by 28 U.S.C. Section 2201.

This regulation mirrors the statutory exhaustion requirement in 21 U.S.C. Section 355(q)(2)(B), which applies during the period before FDA has made a final decision on a new drug application. If a petition has been filed that raises issues with that application, but has not yet been resolved, the statute directs the courts to dismiss without prejudice any suit arising -- any suit raising the same issues for failure to exhaust administrative remedies.

Here, Vanda filed such a petition on January 25th of this year, but FDA has made no final administrative decision on it as of yet. Presumably, it will do so within 180 days, as its own regulations require. That said, it does not necessarily follow 21 C.F.R.; Section 10.45(b) bars judicial review of FDA's underlying approval here until the petition is resolved.

At least one court in this district, in a footnote, appeared to take that view. *Teva Pharmaceuticals versus FDA*, 514 F. Supp. 3d 66, at 111, Note 21, as has

already mentioned.

The Supreme Court has stated that: Where the APA applies, an appeal to superior agency authority, which I understand to mean administrative exhaustion, is a prerequisite to judicial review only when expressly required by statute or when an agency rule requires appeal before review and the administrative action is made inoperative pending that review. That cite is from *Darby v. Cisneros*, 509 U.S. 137, at 154.

Because this is an APA action, and because Vanda's pending petition does not render inoperative FDA's underlying approval, I am not prepared to dismiss Vanda's suit for failure to exhaust at this stage.

Second, defendants argue that Vanda's petition may have rendered FDA's decision to approve Teva's ANDA nonfinal. D.C. Circuit has held that: A pending petition for administrative reconsideration renders the underlying agency action nonfinal and, hence, unreviewable with respect to the petitioning party; that's *TeleSTAR, Inc. v. FCC*, 888 F.2d 132, at 133.

I agree with my colleague Judge Sullivan that it does not matter what administrative petition is called if it, in fact, seeks reconsideration of an FDA decision, then it renders the underlying decision unviewable. That was Judge Sullivan in *King versus Leavitt*, 475 F.Supp.2d 67,

at 72.

Here, too, however, it is unclear whether Vanda is effectively a petitioner for administrative reconsideration. The regulation governing Vanda's petition, 21 C.F.R. Section 10.25, is intended where a party asks FDA to: Amend or revoke a regulation or order, or to take or refrain from taking any other form of administrative action. And, on the one hand, Vanda's petition expressly invokes FDA's inherent power to reconsider and change a decision if it does so within a reasonable period of time.

On the other hand, Vanda points out that, unlike the petitioners in *TeleSTAR* and *Leavitt*, it is not a party to the original decision, and it is asking FDA to take separate action of revoking rather than merely reconsidering its approval of Teva's ANDA. In at least some circumstances, D.C. Circuit has appeared to allow judicial review of agency actions by parties that have simultaneously petitioned the agency to revoke those actions. For example, *County Sovereignty Committee v. Department of State*, 292 F.3d 797, at 799; *Columbia Falls Aluminum Company versus EPA*, 139 F.3d 914, at 919. As a result, I am not certain that Vanda's petition has rendered FDA's underlying approval of Teva's ANDA nonfinal.

With regard to ripeness, defendants contend that this case is not ripe for judicial review until FDA resolves

Vanda's petition.

As the Supreme Court explained in *Abbott Laboratories versus Gardner*, 387 U.S. 136, 148 to 49, the ripeness doctrine operates in this context to prevent the Court through avoidance of premature adjudication from entangling themselves in abstract disagreements over administrative policies, and also to protect the agencies from judicial interference until an administrative decision has been formalized and its effects solved in a concrete way by challenging parties. Under this doctrine, the Court must evaluate both the fitness of the issues for judicial decision and the hardship to the parties of withholding court consideration. That's *Abbott*, at 149.

The fitness of the issues for judicial decision does not clearly counsel dismissal here. The meaning of the "sameness" requirement for generic drug labels, along with that requirement's different-manufacturer exception, are largely issues of legal interpretation. Further, explanation and reasoning from FDA might shed some additional light on its decision, but the essential facts -- the FDA approved Teva's label and that the label lacks Braille and accompanying statements -- are not really in dispute.

As for the hardships resulting from delaying judicial consideration, I will discuss those next for

purposes of analyzing the irreparable harm factor of its preliminary injunction standard. But, for now, I am not convinced to outright reject Vanda's suit or motion on grounds of exhaustion, finality, or ripeness.

That brings me to the standard for preliminary injunction. Ultimately, I conclude that Vanda has failed to meet that standard here.

I will start with irreparable harm. Vanda advanced two theories of irreparable harm but both, in my opinion, are flawed.

First, Vanda argues that Teva's labels will result in harm to patients which will, in turn, diminish the goodwill Vanda has built around tasimelteon during the years it's been the exclusive manufacturer. I will set aside for a moment the contested claim that Teva's labels are unsafe.

Even assuming there is a risk to public safety and that a "loss of goodwill" in a market is a form of irreparable harm, the chain of speculation required for harm to accrue to Vanda is simply too long. For Vanda to suffer meaningful reputational harm, a significant portion of Non-24 patients would have to: One, switch from Vanda's Hetlioz to Teva's tasimelteon; two, make a mistake in using Teva's drug as a result of the missing Braille; three, suffer harm as a result of their mistaken use of Teva's drug; and four, irrationally blame that harm on Vanda rather

than Teva. That does not meet the preliminary injunction requirement that a threatened harm be: Certain and great, actual and not theoretical, and so imminent that there is a clear and present need for equitable relief. I am quoting from *League of Women Voters of U.S. versus Newby*, 838 F.3d 1, at 7-8.

Second, Vanda contends that it will suffer economic harm from Teva's entry into the tasimelteon market and it will not be able to recover that money from FDA.

However, my view, along with most of my colleagues on this court, is that even unrecoverable economic losses do not automatically constitute irreparable harm but, instead, must be sufficiently severe to warrant emergency relief. That's from *Save Jobs USA versus U.S. Department of Homeland Security*, 105 F. Supp. 3d 108, at 115. It is not clear that the losses here are that severe, that is, that they threaten the very existence of the movant's business. I am citing from *Wisconsin Gas Company versus Federal Regulatory Energy Commission*, 758 F.2d 669, at 674.

The most Vanda officials allege is the fact that it is unclear that Vanda will have sufficient financial resources to meet Vanda's long-term operating needs or continue operations in their current form. But uncertain predictions about Vanda's reduced long-term profits or potential need to downsize are not enough to justify the

extraordinary, short-term remedy of a preliminary injunction. At worst, denial of the preliminary injunction here will force Vanda to wait up to 180 days for a decision from FDA; Vanda has not clearly shown any existential threats to their business in that time frame.

Moreover, as the FDA points out, at page 39 of its opposition, all of Vanda's predicted economic losses stem from the fact that they will have generic competition -- not from the fact that the generic competition does not have Braille on its labeling. So if Teva added Braille to its labeling, Vanda would likely suffer the exact same injuries. Thus, even the correction of FDA's alleged errors and the grant of Vanda's requested relief would only delay those injuries, not prevent them. In light of these facts, Vanda's predicted economic losses do not rise to the level of irreparable harm.

Neither -- and so with regard to equities and public interest, neither the balance of equities nor the public interest weigh in favor of a preliminary injunction here.

As I have just explained, the threat of harm to Vanda is significantly less than what it asserts. Its risk of reputational damage is speculative, and its risk of economical losses is neither existential in the foreseeable future, nor redressable by ordering FDA to require Braille

on Teva's tasimelteon labels.

In addition, Vanda's economic losses if an injunction is not granted are counterbalanced by Teva's economic losses if an injunction is granted. Invalidating FDA's approval of the ANDA and ordering the recall of Teva's tasimelteon products would not only impose significant costs on Teva now, but would also deprive Teva of valuable future marketing opportunities, particularly during its ongoing, nontolling 180-day period of marketing exclusivity. The potential economic losses on both sides of the equation are not identical, but they further undermine Vanda's ability to make a clear showing on the equities.

More importantly, however, the public interest weighs against granting the preliminary injunction. In designing the ANDA approval regime, Congress sought to get generic drugs into the hands of patients at reasonable prices fast. I am quoting from *In re Barr Labs.*, 930 F.2d 72, at 76. Vanda does not contest this clear congressional intent, nor could it.

Consumers, plainly, have a strong interest in the increased availability and decreased prices provided by generic drugs. My colleagues on the district court have routinely concluded, therefore: It is not in the public interest for the Court to grant a preliminary injunction preventing generic drugs from being sold on the market.

ViroPharma, Inc. v. Hamburg, 898 F. Supp. 2d 1, 30; *Hi-Tech Parmacal Co., Inc. v. FDA*, 587 F. Supp. 2d 1, 12-13; *Biovail Corp. v. FDA*, 519 F. Supp. 2d 39, 50.

The main countervailing public interest that Vanda asserts is patient safety. Vanda claims the lack of Braille on Teva's label: Puts blind people at significant risk of struggling to differentiate between multiple medications or failing to administer the proper dose. But Vanda does not explain how dangerous those consequences would be, if at all, much less provide concrete evidence of that danger. So even relying on Vanda's evaluation, the actual risks to patient safety are far from clear.

Moreover, Vanda's evaluation is not the only one before the Court. FDA has also reviewed Teva's ANDA, including the label's lack of Braille, and concluded that the drug would be safe for marketing to blind patients.

FDA is the agency Congress has tasked with evaluating drug safety, and courts must accord a high level of deference to this kind of scientific judgment within FDA's area of expertise; *Rempfer v. Sharfstein*, 583 F.3d 860, at 867. I, accordingly, grant significant weight to FDA's determination and cannot conclude that safety concerns clearly show a preliminary injunction to be in the public interest here.

Finally, I note that the nature of the relief

Vanda seeks is further reason for hesitation about granting a preliminary injunction here.

As I have already observed, the legal burden on a movant is particularly heavy where they seek an injunction to change the status quo rather than preserve it. That is the situation here, unlike the two cases Vanda cites as precedent.

In both *Bayer HealthCare, LLC v. FDA* and *Collagenex Pharmaceuticals v. Thompson*, the generic product had not fully launched into the market, if at all, at the time of the court's order. As a result, the movants sought only to vacate or prevent FDA's approval.

By contrast, here, Teva's tasimelteon is already out on the market. And Vanda does not ask the Court to simply order the FDA to require Braille and the accompanying statements on Teva's labels going forward, and not even merely to vacate FDA's approval but, also, to order the FDA to re-call all of Teva's tasimelteon already sold and distributed. I am not aware of any case -- and Vanda does not cite any -- in which a court has issued that kind of preliminary, mandatory injunction to force an approved generic drug off the market in this kind of situation. The circumstances of this case do not persuade me that I should be the first.

Because I conclude that Vanda has failed to meet

its burdens with respect to clear showings on irreparable harm, the balance of equities, and the public interest, I do not reach their likelihood of success on the merits.

For these reasons, I will deny Vanda's motion for preliminary injunction, and I will enter an order memorializing this ruling shortly.

All right. Counsel, thank you, all, very much.

This -- obviously, as I said, I did not dismiss this case on the other grounds so the case remains. I will issue, as I said, an order on a preliminary injunction, and then we can move forward from there but I have to return to my jury trial at this point.

Thank you.

MR. BURGESS: Thank you, Your Honor.

MR. BELFER: Thank you, Your Honor.

MR. HUGHES: Thank you, Your Honor.

THE COURTROOM DEPUTY: The parties are excused.

(Whereupon, the proceeding concludes, 1:44 p.m.)

CERTIFICATE

I, ELIZABETH SAINT-LOTH, RPR, FCRR, do hereby certify that the foregoing constitutes a true and accurate transcript of my stenographic notes, and is a full, true, and complete transcript of the proceedings to the best of my ability.

This certificate shall be considered null and void if the transcript is disassembled and/or photocopied in any manner by any party without authorization of the signatory below.

Dated this 16th day of March, 2023.

/s/ Elizabeth Saint-Loth, RPR, FCRR

Official Court Reporter

UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF COLUMBIA

NOVARTIS PHARMACEUTICALS CORPORATION, Plaintiff, v. XAVIER BECERRA, in his official capacity as Secretary of Health and Human Services, *et al.*, Defendants, and MSN PHARMACEUTICALS INC., *et al.*, Intervenor-Defendants.	No. 1:24-cv-02234-DLF

[Proposed] Order Denying Injunction

Before the Court is Novartis's Motion for Temporary Restraining Order or Preliminary Injunction. Based on the parties' filings and the arguments of counsel, the Court finds that Novartis has not shown a likelihood of success on the merits of its claims, will not suffer irreparable harm in the absence of emergency relief, and has not shown that the balance of harms or public interest favor an injunction. It is therefore ORDERED that Novartis's motion is DENIED.

SO ORDERED.

Dated: _____

_____
Hon. Dabney L. Friedrich
United States District Judge