



Jin Chon
Takeda Pharmaceuticals U.S.A., Inc.
One Takeda Parkway
Deerfield, IL 60015

Re: Docket No. FDA-2019-P-0837

JUL 18 2019

Dear Mr. Chon:

This letter responds to the citizen petition you submitted on behalf of Takeda Pharmaceuticals U.S.A., Inc. (Takeda) and H. Lundbeck A/S (Lundbeck, individually or together with its affiliates) and received by the Agency on February 20, 2019 (Petition). You request that FDA require that the labeling for any abbreviated new drug application (ANDA) or any application submitted under the pathway described in section 505(b)(2) of the Federal Food, Drug and Cosmetic Act (FD&C Act) that references Trintellix (vortioxetine) tablets (new drug application (NDA) 204447) include the following information in the Trintellix labeling regarding the incidence of treatment-emergent sexual dysfunction (TESD) with vortioxetine and certain selective serotonin reuptake inhibitors (SSRIs):

6 ADVERSE REACTIONS

6.1 Clinical Studies Experience

Sexual Dysfunction

In addition to the data from the [major depressive disorder (MDD)] studies mentioned below, TRINTELLIX has been prospectively assessed for its effects in MDD patients with existing TESD induced by prior SSRI treatment

14 CLINICAL STUDIES

Prospective Evaluation of Treatment Emergent Sexual Dysfunction (TESD)

Two, randomized, double-blind, active-controlled studies were conducted to prospectively compare the incidence of TESD between TRINTELLIX and SSRIs via a validated self-rated measure of sexual function, the Changes in Sexual Functioning Questionnaire Short Form (CSFQ-14)

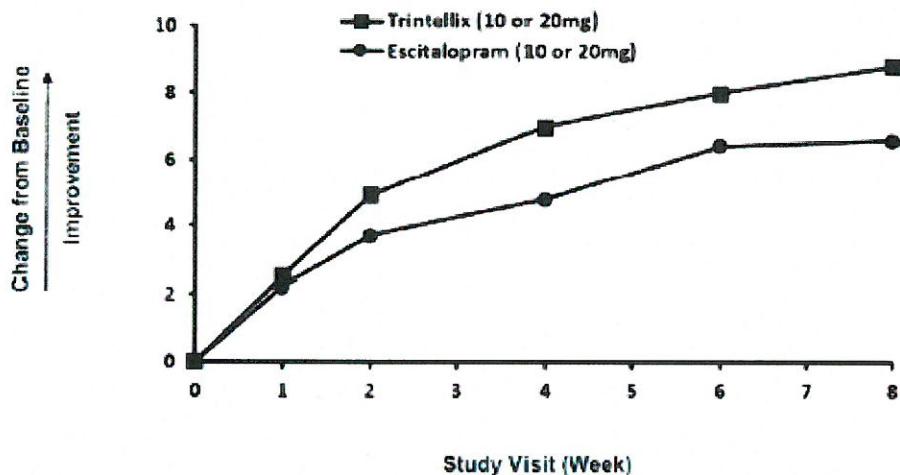
Effect of Switching from SSRI to TRINTELLIX on TESD

The effect of TRINTELLIX on TESD induced by prior SSRI treatment in MDD patients whose depressive symptoms were adequately treated was evaluated in an eight-week,

randomized, double-blind, active-controlled (escitalopram), flexible-dose study (Study 10). Patients taking citalopram, sertraline, or paroxetine for at least eight weeks duration and who were experiencing sexual dysfunction attributed to their SSRI treatment were switched to TRINTELLIX (n=217) or escitalopram (n=207). For both TRINTELLIX and escitalopram, patients were started on 10 mg, increased to 20 mg at Week 1, followed by flexible dosing. The majority of subjects received the 20 mg dose of TRINTELLIX (65.6%) or the 20 mg dose of escitalopram (71.9%) during the study.

Improvement in TESD induced by prior SSRI treatment in subjects switched to TRINTELLIX was superior to the improvement observed in those subjects who switched to escitalopram (2.2 point improvement vs escitalopram on the change from Baseline in CSFQ-14 total score, with 95% confidence interval 0.48 – 4.02), after eight weeks of treatment, although both drugs maintained the subjects' prior antidepressant response. For change from Baseline in CSFQ-14, see *Figure 7*.

Figure 7. Change from Baseline in CSFQ-14 Total Score by Study Visit (Week) in Study 10



(Petition at 1, 22-23).¹

We have considered your Petition and comments to the docket. For the reasons explained below, your Petition is denied.²

¹ As set forth in section II.A below, we determined that the scope of the information protected by 3-year exclusivity includes information derived from Studies 10 and 11.

² As noted, you request that FDA not approve any application submitted pursuant to section 505(b)(2) of the FD&C Act that relies on Trintellix and omits the protected information in the Trintellix labeling. We note, however, that 505(b)(2) applications are not required to have the same labeling as the listed drug they rely upon. In addition, because 505(b)(2) applications can differ from listed drugs in a variety of ways, we cannot address requests for what labeling would be needed for a 505(b)(2) application as a general matter. If there are any 505(b)(2) applications, we will determine the appropriate labeling based on the individual facts and circumstances of an individual application.

I. BACKGROUND

A. Trintellix

Trintellix is an SSRI approved for “the treatment of major depressive disorder.”³ Takeda holds approved NDA 204447 for Trintellix (vortioxetine) tablets, 5, 10, 15, and 20 milligrams (mg).⁴

Major depressive disorder (MDD) is a serious and life-threatening condition, affecting over 17 million people in the United States and over 300 million people worldwide.⁵ Patients with MDD may be unable to work, maintain relationships, attend to self-care, and in the most severe cases may become hospitalized or attempt or commit suicide.⁶ MDD is considered the leading cause of disability worldwide.⁷ Treatment may include some combination of psychotherapy, pharmacotherapy, psychosocial therapy, or a somatic therapy (e.g., electroconvulsive therapy). FDA has approved a variety of drug products indicated to treat MDD, including SSRIs, other classes of antidepressants (e.g., serotonin-norepinephrine reuptake inhibitors (SNRIs)), and a variety of other antidepressants and augmentation agents. The decision-making process regarding which antidepressant to initiate for treating MDD and which antidepressant to switch to if an initial therapy does not achieve remission and/or provokes adverse events (AEs) is complex. TESD is one of many potential common AEs (such as nausea, diarrhea, headaches, sleep changes, or weight changes) that may occur during treatment with antidepressants, including SSRIs, and thus the issue of reducing the risk of TESD is only one factor among many considered by prescribers and patients. Clinicians and patients together must weigh potential benefits versus risks, including such factors as the severity of the patient’s MDD symptoms, the patient’s degree of functional impairment, various possible AEs, and ways to mitigate any AEs that may occur, when determining the MDD treatment with the best benefit/risk balance for a

and the conditions of use sought in the proposed labeling for a particular application. Therefore, this response focuses solely on your request with respect to ANDAs submitted pursuant to section 505(j) of the FD&C Act.

³ NDA 204447 Approval, Sep. 30, 2013, labeling available at

https://www.accessdata.fda.gov/drugsatfda_docs/label/2013/204447s000lbl.pdf. Trintellix was originally approved under the proprietary name Brintellix. FDA approved the name change to Trintellix to decrease the risk of prescribing and dispensing errors resulting from name confusion with the blood-thinning medicine Brilinta (ticagrelor). FDA Drug Safety Communication: FDA Approves Brand Name Change for Antidepressant Drug Brintellix (Vortioxetine) To Avoid Confusion With Antiplatelet Drug Brilinta (Ticagrelor), May 2, 2016 <https://www.fda.gov/Drugs/DrugSafety/ucm497942.htm>; see FDA Approval Letter NDA 204447/S-007 (May 2, 2016) https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2016/204447Orig1s007ltr.pdf. This response refers to NDA 204447 as Trintellix, including during the period of time when it was known as Brintellix.

⁴ The 2013 Trintellix approval included a 15 mg tablet but it has never been marketed by Takeda. See Determination that TRINTELLIX (Vortioxetine Hydrobromide) Oral Tablet, EQ 15 Milligram Base, Was Not Withdrawn From Sale for Reasons of Safety or Effectiveness, 82 FR 55378 (Nov. 21, 2017).

⁵ <https://www.nimh.nih.gov/health/statistics/major-depression.shtml>, accessed July 11, 2019.

⁶ World Health Organization. Depression and other common mental disorders. Global Health Estimates. (Geneva: World Health Organization, 2017.)

⁷ <https://www.who.int/news-room/fact-sheets/detail/depression>, accessed July 11, 2019.

particular patient.⁸

Determining the relationship between any sexual dysfunction and antidepressant therapy is complex. Sexual dysfunction may be a symptom of MDD itself, and thus a prescriber may be able to attribute sexual dysfunction to an antidepressant therapy, such as vortioxetine, as opposed to MDD, only after the patient stabilizes and the acute episode of MDD has abated.⁹ If the patient experiences sexual dysfunction after the acute episode of MDD has passed, the sexual dysfunction might be attributed to antidepressant therapy (because MDD symptoms, such as loss of interest in sex, have presumably been resolved).¹⁰

Given the potential effect of concerns about sexual dysfunction AEs on willingness to initiate antidepressant drug therapies and of sexual dysfunction on treatment adherence, FDA has acknowledged the value of studying the comparative association between different antidepressant treatments, including SSRIs, and sexual dysfunction, including TESD. At an end-of-Phase II meeting for Trintellix in 2008, FDA stated that “if [the Sponsor] were able to show superiority to an active comparator . . . and show non-inferiority to placebo for their drug, they may be able to add such findings to labeling.”¹¹

Because sexual dysfunction can be a symptom of MDD, a placebo-controlled trial was desired in order to distinguish differential association with sexual dysfunction from differential MDD treatment success. Without placebo-controlled studies, it would be difficult to determine whether an observed lower rate of sexual dysfunction with one SSRI over another was attributable to a lower incidence of TESD or greater improvement in the underlying depressive disorder.

In 2013, FDA approved NDA 204447 for Trintellix (vortioxetine) tablets, 5, 10, 15, and 20 mg,¹² *without* the currently protected information regarding the incidence of TESD in vortioxetine and certain other SSRIs.

On October 18, 2018, FDA approved a supplemental NDA (NDA 204447/S-017) based on clinical data from two randomized, double-blind, active controlled studies that assessed sexual function using the Changes in Sexual Functioning Questionnaire Short Form (CSFQ-14).

⁸ See e.g., The American Psychiatric Association, Practice Guideline for the Treatment of Patients with Major Depressive Disorder (APA MDD Practice Guideline) (3rd Ed.) at 20-22, available at https://psychiatryonline.org/pb/assets/raw/sitewide/practice_guidelines/guidelines/mdd.pdf.

⁹ See id. at 36-38.

¹⁰ See id.

¹¹ FDA Drug Approval Package, Administrative Document(s) & Correspondence at 178 (Memorandum of Meeting Minutes, End of Phase II Meeting at 7 (Feb. 5, 2008)) https://www.accessdata.fda.gov/drugsatfda_docs/nda/2013/204447Orig1s000AdminCorres.pdf.

¹² The 2013 Trintellix approval letter is available at https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2013/204447Orig1s000ltr.pdf. In addition, the 2013 Trintellix approval included a 15 mg tablet that was never marketed by Takeda. See Determination that TRINTELLIX (Vortioxetine Hydrobromide) Oral Tablet, EQ 15 Milligram Base, Was Not Withdrawn From Sale for Reasons of Safety or Effectiveness, 82 FR 55378 (Nov. 21, 2017).

To support NDA 204447/S-017, Takeda first completed Study 318 (also referred to as Study 10 in the Trintellix labeling), that compared the incidence of TESD with a switch to vortioxetine versus escitalopram in patients with stable MDD currently taking citalopram, sertraline, or paroxetine and experiencing sexual dysfunction. In Study 10, vortioxetine demonstrated greater improvement in sexual dysfunction scores on the CSFQ-14 in a prospective parallel-group, as compared to escitalopram. Subjects with TESD and stably-treated MDD entered the study having taken citalopram, sertraline, or paroxetine for at least 8 weeks, then were randomized to switch to vortioxetine or escitalopram, both starting at a 10 mg dose and titrated to a 20 mg dose, as tolerated. (In the vortioxetine group, 65.6% of subjects tolerated 20 mg; in the escitalopram group, 71.9% of subjects tolerated 20 mg.) At week 8, vortioxetine demonstrated statistically significantly greater improvement in CSFQ-14 scores as compared to escitalopram. Subjects' CSFQ-14 scores also improved on escitalopram (by a mean of 6.6 points compared to 8.8 points for vortioxetine); the study authors prespecified that a change of 2 to 3 points on the CSFQ-14 would be considered clinically significant.

At a 2015 meeting with FDA's Division of Psychiatry Products (DPP) regarding the submission of NDA 204447/S-017, DPP noted that two positive trials or a justification for reliance on a single trial would be necessary to support a labeling claim regarding TESD.¹³

Thereafter, Takeda completed Study 4001 (also referred to as Study 11 in the Trintellix labeling), that compared the incidence of TESD using the CSFQ-14 outcome measure between vortioxetine 10 and 20 mg, paroxetine 20 mg, and placebo in healthy subjects. At Week 5, vortioxetine 10 mg was associated with significantly less sexual dysfunction than paroxetine 20 mg, but vortioxetine 20 mg was not.

Based on the data presented in Studies 10 and 11 submitted in the supplemental NDA, FDA approved the addition of information regarding TESD to the Trintellix labeling. The approved indication—the treatment of MDD—remained unchanged. The substantive information in the supplemental NDA was added to the prescribing information in Section 6, ADVERSE REACTIONS, and Section 14, CLINICAL STUDIES.¹⁴

Trintellix received 3-year Hatch-Waxman exclusivity under sections 505(j)(5)(F)(iv) and 505(c)(3)(E)(iv) of the FD&C Act for the supplemental NDA, as indicated in FDA's publication, *Approved Drug Products With Therapeutic Equivalence Evaluations* (the Orange Book), and was assigned exclusivity code M-234: "Update to the prescribing information for vortioxetine on treatment-emergent sexual dysfunction comparing vortioxetine and SSRIs."¹⁵ This exclusivity

¹³ See, e.g., Section 505(d) of the FD&C Act; 21 CFR Section 314.126.

¹⁴ See Trintellix Prescribing Information (Oct. 2018) available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/204447s017lbl.pdf.

¹⁵ The Orange Book is available at <http://www.accessdata.fda.gov/scripts/cder/ob/>. The scope of exclusivity is determined by the nature of the new clinical investigations essential to approval of the application or supplement, and not by the exclusivity code that is used as shorthand to describe that approval in the Orange Book. See Orange Book, Patent and Exclusivity Information Addendum, at AD 1 (39th ed. 2019), available at <https://www.fda.gov/media/71474/download>.

will expire on October 19, 2021.

U.S. Patent No. 9,278,096 (the '096 patent) is listed in the Orange Book in connection with Trintellix. The use code for the '096 patent is U-2436, "use in the treatment of [MDD] to improve [TESD] induced by prior serotonin reuptake inhibitor treatment."¹⁶ According to the information you submitted to the Orange Book, the current expiration date of the '096 patent is March 21, 2032.

B. Legal and Regulatory Background

1. *Hatch-Waxman Amendments, Patent Listing, and 3-Year Exclusivity*

A sponsor seeking to market a brand-name or innovator drug must submit an NDA to the FDA for review. NDAs are approved under section 505(c) of the FD&C Act. Generally, FDA will approve an NDA if the information and data provided by the applicant demonstrate that the drug product is safe and effective for the conditions prescribed, recommended, or suggested in the proposed labeling.¹⁷

The Drug Price Competition and Patent Term Restoration Act of 1984 (Hatch-Waxman Amendments)¹⁸ amended the FD&C Act to add section 505(b)(2) and 505(j), as well as other conforming amendments. The Hatch-Waxman Amendments reflect Congress's efforts to balance the need to "make available more low cost generic drugs by establishing a generic drug approval procedure" with new incentives for drug development in the form of exclusivity and patent term extensions.¹⁹ Under section 505(j) of the FD&C Act, an applicant may submit an ANDA for approval of a generic version of a listed drug approved under section 505(c) of the FD&C Act.²⁰ The ANDA applicant must identify the listed drug on which the applicant seeks to rely for approval. The listed drug an ANDA applicant relies on for approval is referred to as the

¹⁶ In this response we are focusing on whether an ANDA applicant can carve out the 3-year Hatch-Waxman exclusivity under section 505(j)(5)(F)(iv) associated with the approval of the supplemental NDA and not on the precise scope of any carve-out that would be necessitated by a section viii statement for U-2436 for the '096 patent in the absence of a three-year Hatch-Waxman exclusivity carve-out. This is appropriate because we have determined that any labeling carve-out necessitated by the 3-year Hatch-Waxman exclusivity would be at least as broad as (and would subsume) any carve-out necessitated by the '096 patent. Thus, were an ANDA applicant referencing Trintellix and seeking to carve out the information protected by 3-year Hatch-Waxman exclusivity, to also make a section viii statement that it is not seeking approval for the method of use described in use code U-2436, we expect that the labeling would be identical to the labeling for an ANDA applicant that is only omitting the information protected by the 3-year exclusivity under section 505(j)(5)(F)(iv). However, we are not prospectively determining the scope of the carve-out from the Trintellix labeling that would be necessary for an ANDA making a section viii statement regarding a method of use described by use code U-2436 when the 3-year Hatch-Waxman exclusivity expires and only the patent protection remains.

¹⁷ See sections 505(b)(1), 505(c), and 505(d) of the FD&C Act and part 314 (21 CFR part 314).

¹⁸ Public Law 98-417 (1984).

¹⁹ See House Report No. 98-857, part 1, at 14-15 (1984), reprinted in 1984 U.S.C.C.A.N. 2647 at 2647-2648.

²⁰ Sections 505(j)(1) and (j)(7) of the FD&C Act.

*reference listed drug or RLD.*²¹ The ANDA approval process allows an ANDA applicant to rely on FDA's previous finding of safety and effectiveness for the RLD rather than requiring the ANDA applicant to repeat the clinical trials conducted for the RLD and independently demonstrate the safety and effectiveness of its proposed drug product. To rely on such a finding, the ANDA applicant must show that its proposed drug product is the same as the RLD in many respects (including active ingredient, dosage form, strength, route of administration, and, with certain exceptions, labeling), and that its proposed drug product is bioequivalent to the RLD.²²

The timing of ANDA approval depends on, among other things, relevant exclusivity and any patent protection for the RLD and on whether the ANDA applicant challenges those patents or seeks approval for uses covered by exclusivity or a method of use patent.²³ The ANDA applicant must include an appropriate patent certification or statement for each patent that claims the RLD or a method of using the RLD for which the applicant is seeking approval and for which information is required to be filed under section 505(b)(1) or 505(c)(2) of the FD&C Act. For each unexpired patent listed in the Orange Book, the ANDA applicant must submit either a paragraph III certification (which will delay approval until the date on which such patent will expire), a paragraph IV certification (certifying that such patent is invalid or will not be infringed by the manufacture, use, or sale of the drug product for which the ANDA is submitted), or, with respect to a method of use patent, a statement (known as a section viii statement) that the patent does not claim a use for which the ANDA applicant is seeking approval.²⁴

The Hatch-Waxman Amendments also include provisions for periods of exclusivity for certain innovations and for changes to approved drugs. A 3-year exclusivity period is provided for certain changes to an approved drug. Under section 505(j)(5)(F)(iii),²⁵ if an original application is approved "for a drug, which includes an active ingredient (including any ester or salt of the active ingredient) that has been approved in another application approved under [section 505(b)]" and "contains reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant," FDA may not approve an ANDA "for the conditions of approval of such drug . . . before the expiration of three years from the date of the approval of the application."²⁶ Under 21 CFR 314.108(b)(5)(ii) (FDA's regulation implementing section 505(j)(5)(F)(iv) of the FD&C Act), if a supplemental NDA "contains reports of new clinical investigations (other than bioavailability studies) essential to the approval of the supplement and conducted or sponsored by the person submitting the supplemental NDA," FDA may not approve an ANDA "for a change . . . that relies on the information supporting a change approved in the supplemental NDA" for a period of three years.

²¹ 21 CFR Section 314.3(b).

²² See section 505(j)(2)(A) of the FD&C Act.

²³ See sections 505(b)-(c), (j)(2)(A)(vii), (j)(2)(A)(viii), and (j)(5)(B) of the FD&C Act.

²⁴ See sections 505(j)(2)(A)(vii)(III)-(IV) and 505(j)(2)(A)(viii) of the FD&C Act. If an ANDA includes a statement that the patent does not claim a use for which the ANDA applicant is seeking approval, then the ANDA will be accompanied by labeling that includes a corresponding labeling carve-out. See 21 CFR 314.94(a)(8)(iv).

²⁵ A parallel provision at section 505(c)(3)(E)(iii) of the FD&C Act applies to 505(b)(2) applications.

²⁶ See also 21 CFR 314.108(b)(4).

2. *“Same Labeling” Requirement for Products Approved in ANDAs and Permissible Carve-Outs*

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

information to show that the labeling proposed for the new [generic] drug is the same as the labeling approved for the listed drug . . . except for changes required because of differences approved under [section 505(j)(2)(C) of the FD&C Act] or because the new [generic] drug and the listed drug are produced or distributed by different manufacturers.”²⁷

A parallel provision appears in section 505(j)(4)(G) of the FD&C Act.²⁸

Although the requirements set forth in sections 505(j)(2)(A)(v) and 505(j)(4)(G) are known as the “same labeling” requirements, they do not require that a generic drug’s labeling be identical to that of the listed drug it references in every respect. Instead, these provisions reflect, among other things, Congress’s intent that the generic drug be safe and effective for each condition of use prescribed, recommended, or suggested in the generic drug labeling without requiring that an ANDA be approved for each condition of use for which the listed drug is approved. In describing the Hatch-Waxman Amendments, Congress explicitly acknowledged that “the bill permits an ANDA to be approved for less than all of the indications for which the listed drug has been approved.”²⁹

In interpreting the statutory exception to the same labeling requirement, which allows certain labeling differences because the proposed ANDA and the listed drug are “produced or distributed by different manufacturers,” among other things, the regulations at § 314.92(a)(1) (21 CFR 314.92(a)(1)) explicitly state that a proposed generic drug product must have the same conditions of use as the listed drug, except that “conditions of use for which approval cannot be granted *because of exclusivity* or an existing patent may be omitted.”

Similarly, § 314.94(a)(8)(iv) (21 CFR 314.94(a)(8)(iv)) sets forth some examples of permissible differences in labeling that may result because the generic drug product and listed drug are produced or distributed by different manufacturers. Permissible differences include, but are not

²⁷ See also 21 CFR Sections 314.92(a)(1), 314.94(a)(4)(i), 314.94(a)(8)(iv), 314.127(a)(2), and 314.127(a)(7).

²⁸ Section 505(j)(4)(G) of the FD&C Act provides that FDA shall approve an ANDA unless, among other things, “the information submitted in the application is insufficient to show that the labeling proposed for the drug is the same as the labeling approved for [the listed drug] except for changes required because of differences approved under [an ANDA suitability petition] or because the drug and the listed drug are produced or distributed by different manufacturers.”

²⁹ H.R. Rep. No. 98-857, pt.1, at 2; see also id. at 21 (“The [ANDA] applicant need not seek approval for all of the indications for which the listed drug has been approved.”).

limited to, the following:

[D]ifferences in expiration date, formulation, bioavailability, or pharmacokinetics, labeling revisions made to comply with current FDA labeling guidelines or other guidance, or *omission of an indication or other aspect of labeling protected by patent or accorded exclusivity under section 505(j)(5)(F) of the [FD&C Act]*.³⁰

The regulations at § 314.127(a)(7) (21 CFR 314.127(a)(7)) further provide that, to approve an ANDA containing proposed labeling that omits “aspects of the listed drug’s labeling [because those aspects] are protected by patent, or by exclusivity,” we must find that the “differences do not render the proposed drug product less safe or effective than the listed drug for all remaining, non-protected conditions of use.” In practice, when determining how to carve out language from an ANDA’s labeling to give effect to the RLD’s 3-year exclusivity, FDA examines the current labeling of the RLD and makes any appropriate omissions of exclusivity-protected information.³¹ It then determines whether the resulting labeling differences would render the proposed generic product less safe or effective than the RLD for the remaining non-protected conditions of use.³²

Thus, starting with the currently approved labeling for the RLD, these provisions specifically affirm that ANDA applicants may carve out from their proposed labeling any patent- or exclusivity-protected indication or other aspect of labeling and obtain approval for the remaining non-protected conditions of use if the ANDA product would remain no less safe and effective than the RLD for the remaining non-protected conditions of use after removal of the protected information.

Relevant case law affirms an ANDA applicant’s ability to carve out protected labeling without violating the “same labeling” requirement. For example, in *Bristol-Myers Squibb Co. v. Shalala*, 91 F.3d 1493 (D.C. Cir. 1996), the D.C. Circuit ruled that “the statute expresses the legislature’s concern that the new generic be safe and effective for each indication that will appear on its label; whether the label for the new generic lists every indication approved for use of the pioneer is a matter of indifference.”³³ Similarly, in *Sigma-Tau Pharmaceuticals, Inc. v. Schwetz*, 288 F.3d 141 (4th Cir. 2002), the Fourth Circuit upheld the right of an ANDA applicant to carve out an indication protected by orphan drug exclusivity as a permissible labeling difference because of a difference in manufacturer.³⁴ Sigma-Tau Pharmaceuticals, Inc. (Sigma-Tau) argued that FDA was obligated to look beyond the labeling an ANDA applicant proposed to use in determining whether a generic drug would violate an innovator’s exclusivity. The court stated

³⁰ § 314.94(a)(8)(iv) (21 CFR 314.94(a)(8)(iv)) (emphasis added).

³¹ § 314.94(a)(8)(i)(iv) (21 C.F.R. 314.94(a)(8)(i)(iv)).

³² § 314.127(a)(7) (21 C.F.R. 314.127(a)(7)).

³³ *Bristol-Myers Squibb Co. v. Shalala*, 91 F.3d 1493, 1500 (D.C. Cir. 1996). See also *Spectrum Pharm., Inc. v. Burwell*, 824 F.3d 1062, 1066 (D.C. Cir. 2016) (explaining that the D.C. Circuit has “approved FDA’s general approach to labeling carve-outs as an acceptable interpretation of the [FD&C Act]” and upholding FDA’s approval of a generic drug with an indication protected by orphan exclusivity carved out).

³⁴ *Sigma-Tau Pharms., Inc. v. Schwetz*, 288 F.3d 141, 148, n. 3 (4th Cir. 2002).

that Sigma-Tau’s argument would extend exclusivity beyond what Congress intended and “frustrate the longstanding practice of Congress, the FDA, and the courts not to interfere with physicians’ judgments and their prescription of drugs for off-label uses.”³⁵ The court reasoned that “[Sigma-Tau’s theory] to bar the approval of generic drugs, even for unprotected indications[. . . [would add] a huge evidentiary hurdle to the generic drug approval process [and] would be profoundly anti-competitive.”³⁶

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

II. DISCUSSION

You contend that the protected information in the Trintellix labeling informs prescribers that vortioxetine has a low association with sexual dysfunction and therefore that omitting the protected information from the labeling for a generic vortioxetine product would render that product less safe or effective than Trintellix for the remaining, non-protected conditions of use. First, you argue that the protected information covered by exclusivity is broader than the condition of use described in the exclusivity code, mitigates the risk of potential nonadherence due to TESD, and provides essential context to the vortioxetine labeling. Second, you contend that vortioxetine ANDA labeling would be less safe or effective without the protected information because the protected information provides essential context and increases prescribers’ ability to select an appropriate antidepressant therapy when initiating treatment and deciding to continue treatment. Third, you argue that requiring generic vortioxetine labeling to include the protected information would be consistent with FDA’s precedents. Thus, you conclude that FDA should not approve a generic vortioxetine product referencing Trintellix without the protected information, effectively blocking all generic vortioxetine products until the expiration of the Trintellix’s exclusivity on October 19, 2021.

For the reasons described below, we disagree. We address each of these arguments in turn.

A. Scope of the 3-Year Exclusivity

As an initial matter, we clarify that Trintellix received 3-year exclusivity for information that was derived from Studies 10 and 11. Under section 505(j)(5)(F)(iv) of the FD&C Act, if FDA approves a supplement that “contains reports of new clinical investigations (other than bioavailability studies) essential to the approval of the supplement and conducted or sponsored by the person submitting the supplement” the Agency cannot “make the approval of an application submitted under this subsection for a change approved in the supplement effective before the expiration of three years” after the approval of the supplement. The statute does not

³⁵ Id. (citations omitted).

³⁶ Id.

expressly describe how FDA should determine the scope of 3-year exclusivity. In interpreting the 3-year exclusivity provisions, however, FDA has explained that “[t]he statute sets up a relationship between the ‘new clinical investigations’ that are ‘essential to the approval of the supplement,’ and the scope of the exclusivity.”³⁷ The scope of the exclusivity is determined by the scope of the new clinical investigations and does not cover aspects of the drug product for which the new clinical investigations were not essential.

As described above, Trintellix received 3-year exclusivity under sections 505(j)(5)(F)(iv) and 505(c)(3)(E)(iv) of the FD&C Act for NDA 204447/S-017. The Trintellix labeling was also updated to incorporate information protected by the 3-year exclusivity. We determined that the scope of the protected information in this supplemental NDA includes information derived from both Studies 10 and 11, as this information was derived from the new clinical investigations in supplement 17 and essential to the approval of supplement 17.

In the Petition, you claim that the 3-year exclusivity FDA recognized for Trintellix for the approved labeling changes relating to Studies 10 and 11 protects not only information regarding patients who had experienced *treatment-emergent* sexual dysfunction when taking an SSRI, but also protects information regarding “patients who take TRINTELLIX *regardless of whether they previously took another antidepressant or previously experienced TESD*.³⁸ You state that the protected information “increases prescribers’ ability to select an appropriate antidepressant therapy, which mitigates the risk of potential nonadherence due to TESD.”³⁹ You claim that the protected information “functions as a corrective lens”⁴⁰ that prevents a prescriber from being misled when considering vortioxetine for a patient “regardless of whether the patient previously took a serotonin reuptake inhibitor or previously experienced TESD, and regardless of the reason why a patient may have switched from another antidepressant.”⁴¹

1. *Trintellix Exclusivity Is Not Broader Than the Clinical Investigations Essential to Approval of Supplement 17*

We disagree with your assertion that the protected information extends to conditions of approval other than TESD. As described above, Trintellix received 3-year Hatch-Waxman exclusivity under section 505(j)(5)(F)(iv) of the FD&C Act for sNDA 204447-017, as indicated in the Orange Book by the exclusivity code M-234, “update to the prescribing information for vortioxetine on treatment-emergent sexual dysfunction comparing vortioxetine and SSRIs.” The protected information is determined by the clinical investigations that were conducted and extends to information added to labeling regarding patients who experience TESD. As a general matter, and as discussed in more detail below, we reject your assertion that the Trintellix

³⁷ See *AstraZeneca Pharms. LP v. FDA*, 872 F. Supp. 2d 60, 80 (D.D.C. 2012); see also § 314.108 (defining “new clinical investigation” and “essential to approval”).

³⁸ Petition at 2 (emphasis added); see also id. at 14, 16.

³⁹ Id. at 2.

⁴⁰ Id. at 12.

⁴¹ Id.

exclusivity extends to information regarding “patients who take TRINTELLIX regardless of whether they previously took another antidepressant or previously experienced TESD.”⁴²

2. *The Protected Information Does Not Include Information on Treatment Adherence*

You contend that the protected information would increase the ability of health care practitioners to make prescribing decisions that would increase the likelihood of treatment adherence.⁴³ However, you have not provided any evidence from clinical investigations demonstrating any increase in treatment adherence.

Therefore, we reject your contention that Trintellix’s lower degree of treatment-emergent sexual dysfunction necessarily improves treatment adherence. The protected information in the Trintellix labeling⁴⁴ does not include information on whether vortioxetine has a higher likelihood of treatment adherence compared to other SSRIs. Neither Study 10 nor Study 11 sought to compare the relative rates of treatment adherence for vortioxetine and other SSRIs generally, or as adherence relates to TESD. Neither study substantiates your claim that vortioxetine is associated with increased treatment adherence. Therefore, there cannot be an exclusivity-protected condition of approval related to treatment adherence rates. The protected information in the Trintellix labeling does not corroborate your claim that patients on vortioxetine have higher rates of treatment adherence compared with other SSRIs, and thus does not support a determination that a generic without the protected information in its labeling would be less safe and effective than Trintellix for the remaining, non-protected conditions of use.

3. *The Protected Information Does Not Provide “Essential Context” for the ASEX Data in Table 3 of the Trintellix Labeling*

You also argue that omission of the protected information from a vortioxetine ANDA product’s labeling could cause a prescriber to misinterpret the Arizona Sexual Experiences Scale (ASEX) data reported in Table 3 of the Trintellix labeling because the protected information provides “essential context” to comparative data about vortioxetine in MDD patients.⁴⁵ The interpretation of clinical trial information is complex and multifactorial, drawing on a prescriber’s training, experience, and expertise. The protected information in the Trintellix labeling is not essential to understanding the ASEX data in Table 3. Studies 10 and 11 did not utilize the ASEX and the data in Table 3 was present prior to revising the labeling. Moreover, the protected information does not include any statements on the ASEX data reported in Table 3. As you recognize in the petition, the ASEX data in Table 3 includes relatively high rates of sexual dysfunction for the placebo, and you provide no support for your assertion that “the prescriber might not take that

⁴² Id. at 2 (emphasis added); see also id. at 14, 16.

⁴³ Id. at 13-14.

⁴⁴ See Trintellix Prescribing Information, supra n. 14.

⁴⁵ Petition at 12.

fact into consideration.”⁴⁶ In considering whether the omission of certain information from labeling would render a drug product less safe or effective, it is appropriate to assume that prescribers will read the remaining labeling.⁴⁷ Accordingly, we reject your contention that the protected information provides “essential context” on the ASEX data in Table 3 and that the omission of the protected information would cause a provider to misinterpret the data in Table 3. Further, while you appear to argue that the “essential context” provided by the protected information would affect a prescriber’s consideration of vortioxetine in comparison to other treatment options, you do not identify any effect that context would have on how a generic vortioxetine with labeling omitting the protected information is prescribed in comparison to Trintellix. The protected information in the Trintellix labeling thus does not support your assertion that a generic without the protected information in its labeling would be less safe or effective than Trintellix for the remaining, non-protected conditions of use.

B. Omission of the TESD Condition of Use Would Not Render Vortioxetine Less Safe or Effective for the Remaining Approved Condition of Use.

You argue that the protected information improves prescribers’ ability to make decisions that increase safety and efficacy for vortioxetine at two distinct time points: first, when a prescriber initially selects a therapy for a given patient; and second, when sexual dysfunction occurs during treatment of a patient on vortioxetine.⁴⁸ As a result, you conclude that the protected information is essential to the labeling of a generic vortioxetine drug product. As described below, we disagree with these assertions.

As explained in Section I, the decision-making process regarding which antidepressant to initiate for treating MDD and which antidepressant to switch to if a change is warranted is complex and the issue of TESD is only one factor among many that clinicians and patients consider when determining the MDD treatment with the best benefit/risk balance for the patient.⁴⁹

Distinguishing between sexual dysfunction attributable to antidepressant therapy and sexual dysfunction as a symptom of MDD may not be possible until the patient has been stabilized and the acute episode of MDD abated.⁵⁰ If the patient experiences sexual dysfunction after the acute episode of MDD has passed, then the sexual dysfunction might be attributed to antidepressant therapy (because MDD symptoms, such as loss of interest in sex, have presumably been resolved).⁵¹ Thus, as a general matter, any argument that the absence of this particular information alone would be dispositive to a prescriber is unsupported.

⁴⁶ Id.

⁴⁷ See also *Sigma-Tau*, 288 F. 3d at 145-147 (rejecting a foreseeable use test and concluding that an ANDA applicant may carve out a protected indication even when it is likely that the generic drug, once approved, will be used off-label for that indication).

⁴⁸ Petition at 13.

⁴⁹ See e.g., APA MDD Practice Guideline, supra n. 8 at 20-22.

⁵⁰ See id. at 36-38.

⁵¹ See id.

When considering an ANDA with a proposed labeling carve-out, FDA must start with the currently approved RLD labeling, determine what information within it is protected by exclusivity and then assess whether a generic ANDA with this information carved out would be less safe or effective than the RLD for the remaining non-protected conditions of use.⁵²

Here, the addition of labeling describing data from Studies 10 and 11 is the exclusivity-protected change approved in the supplement envisioned by the Hatch-Waxman Amendments. This was the labeling supported by “new clinical investigations” that were “essential” to approval of the supplement, within the meaning of section 505(j)(5)(F)(iv).

1. A Vortioxetine ANDA Product Omitting the Protected Information Would Not Be Less Safe or Effective Than Trintellix for Treatment of MDD During Initial Selection of an Antidepressant Therapy

You argue that a vortioxetine ANDA product omitting the protected information would be less safe or effective than Trintellix for MDD during initial selection of an antidepressant therapy because without the protected information, the labeling would not include any comparative data regarding vortioxetine’s association with sexual dysfunction.⁵³ You assert that in the absence of the protected information, a prescriber considering vortioxetine for treatment of MDD might assume that the association between vortioxetine and sexual dysfunction is stronger than it really is.⁵⁴ Thus, you assert that the protected information makes prescribers more likely to select and initially prescribe vortioxetine because they perceive that the drug is less likely than other SSRIs to cause sexual dysfunction.

We disagree with these assertions. First, as explained in Section II.A, we disagree that the protected information is relevant to initial treatment decisions. The Trintellix labeling in section 6 that was added with supplement 17 explains that the protected information is relevant to patients who have experienced TESD on different SSRIs. It does not compare the rates of TESD among all drug products approved for the treatment of MDD. Second, a prescriber considers many factors when selecting an appropriate antidepressant therapy, including the individual characteristics of the patient and a number of considerations relevant to each potential antidepressant. The possibility of TESD is only one factor among many for a prescriber to consider during initial selection of an antidepressant therapy. The protected information relates to the treatment of patients already suffering from TESD. Since it is not possible to predict which patients will develop TESD, the protected information would not be helpful in initial selection of an antidepressant therapy.⁵⁵

Further, your assertion that the protected information would make prescribers more likely to

⁵² 21 C.F.R. § 314.94(a)(8)(i), (iv); id. § 314.127(a)(7).

⁵³ Petition at 13.

⁵⁴ Id. at 14-15.

⁵⁵ In addition, the study in healthy volunteers does not support your assertion either. The results of Study 11 showed that sexual dysfunction due to vortioxetine 20 mg, which is the target dose for treatment of acute MDD, is not statistically significantly different from paroxetine. Therefore, it is unclear why this information would be relevant at the time of initial treatment when a prescriber would be targeting a dose that does not have a lower rate of TESD.

select vortioxetine when initially selecting an antidepressant therapy is not relevant to the question of whether that information may be carved out from generic vortioxetine labeling. Whether information may be carved out from a generic drug product's labeling depends on whether that generic drug product, prescribed without the omitted labeling, will be no less safe or effective as the RLD for the remaining non-protected conditions of use.

Accordingly, omission of the protected information in the Trintellix labeling would not render a vortioxetine ANDA product less safe or effective than Trintellix for the treatment of MDD during initial selection of an antidepressant therapy.

2. *A Vortioxetine ANDA Product Omitting the Protected Information Would Not Be Less Safe or Effective Than Trintellix for Treatment of MDD When Sexual Dysfunction Occurs During Treatment*

You argue that a vortioxetine ANDA product omitting the protected labeling would be less safe or effective than Trintellix for treatment of MDD at a second time point—during treatment of a patient on vortioxetine.⁵⁶ You also assert that if TESD occurred during vortioxetine therapy, the prescriber would need access to the protected information about the low association of sexual dysfunction (relative to certain SSRIs) to appropriately manage treatment without compromising safety or efficacy.⁵⁷

We disagree with your contentions. As described below, omitting the protected information would not render a vortioxetine ANDA product less safe or effective than Trintellix for treatment of a patient on vortioxetine.

Non-protected information in the labeling states that a dose decrease down to 5 mg/day may be considered for patients who do not tolerate higher doses. In addition, if a patient is experiencing adverse events (AEs) from a drug, standard prescribing practice is to lower the dosage of the drug to determine if a lower dosage mitigates the AEs while maintaining efficacy.⁵⁸ Therefore, a prescriber would understand that he/she could titrate to a lower dose of vortioxetine, such as vortioxetine 10 mg/day, for patients with MDD who respond successfully to vortioxetine 20 mg/day but who experience AEs such as sexual dysfunction.⁵⁹ Accordingly, a prescriber would not need the protected information in the Trintellix labeling to understand that vortioxetine 10 mg/day may be the appropriate dose during antidepressant therapy in a patient with MDD, such as for a patient experiencing sexual dysfunction.

You assert that the protected information from Study 10 demonstrates that there is a low

⁵⁶ Petition at 14.

⁵⁷ Id.

⁵⁸ See APA MDD Practice Guideline supra n. 8 at 17 (“If antidepressant side effects do occur, an initial strategy is to lower the dose of the antidepressant or to change to an antidepressant that is not associated with that side effect.”).

⁵⁹ See Trintellix Prescribing Information, supra n. 14.

association between vortioxetine and sexual dysfunction as compared to certain SSRIs.⁶⁰ In Study 10, vortioxetine demonstrated greater improvement in sexual dysfunction scores on the CSFQ-14 in a prospective parallel-group comparison with escitalopram.⁶¹ However, it should be noted that subjects' CSFQ-14 scores also improved on escitalopram (by a mean of 6.6 points compared to 8.8 points for vortioxetine).⁶² Importantly, although there was (on average) greater improvement in TESD on vortioxetine than escitalopram, the above values represent the mean changes. Numerous patients in the vortioxetine group reported *worsening* on their CSFQ-14 total scores during the study.

You further assert that the protected information from Study 11 demonstrates that there is a low association between vortioxetine and sexual dysfunction as compared to certain SSRIs.⁶³ Study 11 compared TESD by CSFQ-14 scores between vortioxetine 10 and 20 mg, paroxetine 20 mg, and placebo in healthy subjects. At week 5, vortioxetine 10 mg was associated with statistically significantly less sexual dysfunction than paroxetine 20 mg, but vortioxetine 20 mg/day was not statistically significantly different than paroxetine 20 mg.⁶⁴ Thus, the protected information does not describe a benefit at the 20 mg/day dose. Moreover, the remaining information in the labeling specifically instructs a prescriber to, after initiating therapy with vortioxetine 10 mg/day, titrate the dose up to a goal of 20 mg/day because higher doses demonstrated better treatment effects in trials conducted in the United States.⁶⁵ Therefore, prescribers would understand to prescribe the recommended dose of 20 mg/day to provide greater efficacy in treating MDD, but at that recommended dose, vortioxetine did not show a lower incidence of sexual dysfunction.

Study 11 demonstrated that a 10 mg dose of vortioxetine produced less sexual dysfunction than paroxetine 20 mg, as opposed to a 20 mg dose of vortioxetine, which showed no difference in lessening sexual dysfunction as compared to paroxetine 20 mg. This information could be viewed as supporting dose reduction if a patient presents with TESD after their MDD is in remission. However, omitting the protected information from Study 11 would not render an ANDA vortioxetine drug product less safe or effective than Trintellix, because, as discussed above, it is already in the labeling and standard medical practice to consider dose reduction of an antidepressant when a patient has responded to a therapy, has reached remission, and experiences an AE. As noted above, many patients taking vortioxetine will experience sexual dysfunction, and their treatment is often managed in the same way that patients on other antidepressants are managed.

⁶⁰ See id. at 5, 11-12.

⁶¹ Trintellix Prescribing Information supra n. 14, section 14.

⁶² The study authors had determined a change of 2 to 3 points on the CSFQ-14 to be clinically significant.

⁶³ See Petition at 6-7, 12.

⁶⁴ Petition at 6 (quoting Trintellix Labeling, Clinical Studies section) (“TESD with TRINTELLIX 10 mg (n=85), but not with TRINTELLIX 20 mg (n=91), was statistically significantly less than with paroxetine 20 mg (n=83.”).

⁶⁵ Trintellix Prescribing Information, supra n. 14, Dosage and Administration section (noting that “[t]he dose should then be increased to 20 mg/day, as tolerated”).

As part of your argument that the omission of the protected information would render a vortioxetine ANDA product less safe or effective than Trintellix, you cite Khin et al. Khin et al. stated that well-documented evidence of fewer sexual side effects would be an “important clinical benefit.”⁶⁶ Khin does not state that such a “clinical benefit” would inherently make a drug more safe or effective. The Agency has noted that the term “clinical benefit” has a broad meaning, and that “clinical benefits that have supported drug approval have included important clinical outcomes (e.g., increased survival, symptomatic improvement) but have also included effects on surrogate endpoints known to predict clinical benefit (e.g., blood pressure).”

You further contend that commonly held beliefs about serotonergic antidepressants and prescribers’ experience treating patients using such drugs could cause a prescriber to improperly attribute TESD to vortioxetine rather than to some other cause, such as MDD itself.⁶⁷ You argue that without the protected information, the occurrence of TESD might prompt the prescriber to switch the patient to another antidepressant or other therapy.⁶⁸ We reject these arguments as speculative and unsupported. We note that you fail to acknowledge that in fact sexual dysfunction does occur with vortioxetine. In Study 10, slightly more than half (52.1%) of patients who took vortioxetine experienced a return to normal CSFQ scores, indicating that approximately 48% of patients continued to experience sexual dysfunction, and some experienced worsening of sexual dysfunction. Although Study 10 suggests that vortioxetine has a lower association with sexual dysfunction than escitalopram, sexual dysfunction is only one of many potential AEs. Omission of the protected information regarding the lower incidence of one AE (sexual dysfunction) in one drug (vortioxetine) would not, by itself, render a vortioxetine ANDA product less safe or less effective than Trintellix for treatment of MDD.

You assert that omission of the protected information in vortioxetine ANDA labeling may prompt a prescriber to switch a stable patient to a different antidepressant and implement a “cross-taper strategy, where the first antidepressant dose is reduced while the second antidepressant is introduced at a low dose and gradually increased. . . [and] introduces uncertainty into the treatment of a patient who is stable and responding to treatment.”⁶⁹ We find your argument regarding uncertainty arising from cross-tapers during a switch between vortioxetine and other SSRIs to be without merit and does not support your argument that the absence of the omitted information would render the ANDA less safe or effective for the remaining, non-protected condition of use. It is unclear that omission of the protected information would affect the decision of a prescriber to switch therapy because prescribers consider a variety of factors when deciding to switch a stable patient. In addition, non-protected information in Trintellix labeling informs prescribers that “TRINTELLIX can be discontinued abruptly.”⁷⁰ One reason vortioxetine can be discontinued abruptly is that it has a relatively long half-life compared to other serotonergic antidepressants, which protects against withdrawal

⁶⁶ Petition at 4 & n.12 (citation omitted).

⁶⁷ Id. at 13-14.

⁶⁸ Id. at 14-15.

⁶⁹ Petition at 15-16.

⁷⁰ Trintellix Prescribing Information, supra n. 14, Dosage and Administration section.

symptoms.⁷¹ If a prescriber chooses to implement a cross-taper strategy, such a strategy would only enhance the protective effect against withdrawal symptoms. Cross-tapering is commonly done by clinicians for all serotonergic antidepressant switches, specifically to avoid withdrawal symptoms and risk of relapse, and to minimize initial AEs of the new antidepressant.⁷²

Next, you argue that excluding the protected information would decrease the safety and effectiveness of vortioxetine because it is not possible to identify in advance, with certainty, which patients will experience sexual dysfunction that triggers treatment cessation or a switch to another antidepressant.⁷³ We disagree. It is true that clinicians cannot predict in advance, with certainty, which patients will experience TESD, or how any individual patient will respond to different strategies to manage any TESD that occurs. It does not follow from this point, however, that exclusion of the protected labeling information would render a vortioxetine ANDA product less safe or effective than Trintellix. Information that the incidence of TESD is lower on vortioxetine than a particular alternative drug product does not mean that all patients should remain on vortioxetine. Patients taking vortioxetine may still suffer from TESD and switching to a different antidepressant drug might be appropriate for some patients. As stated above, the non-protected information in the Dosage and Administration section of Trintellix labeling indicates that prescribers should consider a dose decrease if AEs occur. Also, as noted previously, if a patient is experiencing AEs from an antidepressant drug, standard prescribing practice is to lower the dosage of the drug to determine if a lower dosage mitigates the AEs.

For these reasons, omission of the protected information would not render a vortioxetine ANDA product less safe or effective than Trintellix for treatment of MDD when sexual dysfunction occurs during treatment.

3. Information Regarding Studies 10 and 11 Are Not Essential for Vortioxetine Labeling

FDA has determined as a scientific matter that it is not necessary to include the information derived from Studies 10 and 11 that was added in sNDA 204447-017 in the labeling for generic vortioxetine. FDA has also determined that generic vortioxetine with the protected information carved out would not be less safe or effective for the remaining non-protected conditions of use than Trintellix. Accordingly, a carve-out of the protected information is permissible in this case.

⁷¹ Trintellix Prescribing Information, see n. 14 section 12.3; see also Smithson J and Mitchell PB, 2015, Chapter 2 – Antidepressants. In: Ray S, editor, Side Effects of Drugs Annual, Amsterdam: Elsevier, 37:15-31; Ogle NR and Akkerman SR, 2012, Guidance for the Discontinuation or Switching of Antidepressant Therapies in Adults, J Pharm Pract, 26(4):389-396.

⁷² Hirsch M, Birnbaum RJ, 2012, Antidepressant Medication in Adults: Switching and Discontinuing Medication. In: Basow DS, editor, UpToDate, Waltham, MA.

⁷³ Petition at 14.

C. Approval of a Vortioxetine ANDA That Omits the Protected Information in the Trintellix Labeling Is Consistent with FDA Precedent

You argue that requiring generic labeling to include the protected information in the Trintellix labeling would be consistent with FDA's precedents.⁷⁴ As explained below, we disagree.

1. Rapamune (sirolimus)

One of the citizen petition responses you cite in support of your Petition involved a proposed carve-out from the labeling for Rapamune (sirolimus).⁷⁵ Rapamune was approved as an immunosuppressive agent indicated for the prophylaxis of organ rejection in patients receiving renal transplants. However, Rapamune in combination with cyclosporine was found to be associated with increased renal function impairment. Based on the results of an adequate and well-controlled clinical trial, the labeling for Rapamune was revised to add information about procedures to withdraw cyclosporine in patients at low to moderate risk for rejection. Those changes received three years of Hatch-Waxman exclusivity.⁷⁶ Rapamune's sponsor submitted a citizen petition in 2003 requesting that FDA refrain from approving an ANDA for sirolimus with labeling that omitted the protected cyclosporine withdrawal information. In granting the petition, we determined that the protected information in the labeling was necessary for safe use, even in the remaining unprotected population (i.e., patients at high risk of immune system reactions) because high-risk patients could be reclassified as low-to-moderate risk and could benefit from information regarding the cyclosporine-sparing regimen.⁷⁷

The circumstances here are different from the circumstances in the Rapamune petition. In the Rapamune example, the protected labeling contained critical prescribing information pertaining to cyclosporine withdrawal that physicians needed to receive to appropriately determine treatment of all indications for sirolimus; on the basis of the protected information, the Rapamune labeling directs prescribers to determine treatment regimes, including whether or not to also prescribe cyclosporine, based on rejection risk classification.⁷⁸ As such, the Agency determined that omitting the protected information in the Rapamune labeling from generic sirolimus labeling would have rendered a generic sirolimus product less safe than Rapamune for the remaining, non-protected conditions of use. In contrast, in the present case, the protected information in the Trintellix labeling would not alter how vortioxetine is used (e.g., affecting the prescribed dosage or precluding combination with certain other drugs). Specifically, unlike the case in Rapamune, excluding the protected information in the Trintellix labeling would not create a risk of inappropriately using the drug because no new instructions for use were added and physicians will continue to consider the potential for TESD as one of the many factors in

⁷⁴ Petition at 16.

⁷⁵ Petition at 16-17 (citing Letter to Michael S. Labson and Elizabeth M. Walsh, Covington & Burling, from Steven K. Galson, M.D., M.P.H., Acting Director, Center for Drug Evaluation and Research (Sep. 20, 2004), Docket No. 2003P-0518/CP1 (Rapamune Response Letter)).

⁷⁶ Rapamune Response Letter at 1-2.

⁷⁷ Id.

⁷⁸ Id. at 3.

choosing a treatment approach for MDD. In addition, other non-protected information that will remain in the labeling will provide information to physicians about lowering the dose to decrease adverse events (including sexual dysfunction). Therefore, as described above, omission of the protected information in the Trintellix labeling would not render a vortioxetine ANDA product less safe or less effective than Trintellix for the remaining, non-protected conditions of use.

2. *Colcrys (colchicine)*

Another citizen petition response you cite in support of your Petition involved a proposed carve-out from the labeling for Colcrys (colchicine).⁷⁹ Based on the results of the AGREE trial, the labeling for Colcrys was revised to add information related to the dosing regimen for colchicine for treatment of acute gout flares. FDA recognized a 3-year period of exclusivity for Colcrys based on the AGREE trial.⁸⁰ Colcrys's NDA holder submitted a citizen petition in 2010 requesting that FDA refrain from approving an ANDA for colchicine with labeling that omitted the protected acute gout flares information. Because FDA determined that omission of the protected information in the Colcrys labeling would render a proposed generic of Colcrys less safe or effective than Colcrys for the remaining, non-protected conditions of use (i.e., prophylaxis of gout flares), FDA granted, in part, the petitioner's request.⁸¹

The circumstances here are different from the circumstances in the Colcrys petition. In the Colcrys Response Letter, FDA stated that the labeling for a single-ingredient colchicine product seeking approval for prophylaxis of gout flares should inform healthcare providers that the lower dose colchicine regimen evaluated in the AGREE trial is adequate to treat an acute gout flare that may occur during chronic colchicine use. That is, on the basis of the protected information the Colcrys labeling directs physicians on the appropriate treatment regime for an acute gout flare experienced during chronic colchicine use. At the time FDA responded to the Colcrys petition, information about the lower-dose colchicine regimen was deemed to be important for decreasing the risk of cumulative toxicity from colchicine.⁸² Unlike Colcrys, the protected information in the Trintellix labeling is not information that addresses a direct safety risk associated with a non-protected indication, but rather a comparison of the risk of one potential adverse event with vortioxetine versus certain alternative antidepressant drug products. Again, unlike Colcrys, the protected information in the Trintellix labeling would not alter how vortioxetine is used (e.g. affecting the prescribed dosage or precluding combination with certain other drugs). Study 11 suggests that a lower dose may reduce the incidence of TESD in certain patients. However, the labeling already included information about reducing the dose for patients experiencing adverse events prior to addition of the protected information. In addition, it is a standard prescribing

⁷⁹ Petition at 17 (Letter to Gary L. Veron, Esq., Sidley Austin LLP, from Janet Woodcock, M.D., Director, Center for Drug Evaluation and Research (May 25, 2011), Docket No. FDA-2010-P-0614 (Colcrys Response Letter)).

⁸⁰ Colcrys Response Letter at 6-7, 22.

⁸¹ Id. at 3.

⁸² FDA subsequently determined, in the context of a single-ingredient colchicine product approved through the 505(b)(2) pathway (Mitigare capsules), that this issue may be addressed by a Limitation of Use statement in product labeling advising that the safety and effectiveness of Mitigare for acute treatment of gout flares during prophylaxis has not been studied.

practice in the treatment for depression to consider lowering the dosage of the drug to determine if a lower dosage reduces the adverse effects while maintaining efficacy.⁸³ Thus, as described above, the omission of the protected language in the Trintellix labeling would not render a vortioxetine ANDA product less safe or effective than Trintellix for the remaining, non-protected conditions of use.

For these reasons, the Rapamune and Colcrys carve-out decisions cited in the Petition do not support your assertion that permitting the omission of the protected information in the Trintellix labeling from the labeling of a vortioxetine ANDA would render the generic less safe or effective than Trintellix for the remaining non-protected conditions of use.

III. CONCLUSION

For the reasons discussed above, your Petition is denied.

Sincerely,



Janet Woodcock, M.D.
Director
Center for Drug Evaluation and Research

⁸³ See APA MDD Practice Guideline, supra n. 8 at 17, 36.