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Submitted via Regulations.gov

Division of Dockets Management
Department of Health and Human Services
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

CITIZEN PETITION

Takeda Pharmaceuticals U.S.A., Inc. (Takeda) and H. Lundbeck A/S (Lundbeck, individually or together with its affiliates) submit this citizen petition under section 505(q) of the Federal Food, Drug, and Cosmetic Act (FDCA), 21 C.F.R. § 10.30, and 21 C.F.R. § 10.31 to request that the Commissioner of Food and Drugs (Commissioner) take the actions identified in section A below. Takeda holds approved New Drug Application (NDA) 204447 for TRINTELLIX® (vortioxetine) tablets. Lundbeck is the assignee and owner of certain patents listed in *Approved Drug Products with Therapeutic Equivalence Evaluations* (the Orange Book) for TRINTELLIX.

Takeda and Lundbeck submit this petition to ensure that the labeling for any vortioxetine product that references or relies upon TRINTELLIX contains all information necessary for the safe and effective use of the proposed product. We are concerned that applicants submitting abbreviated new drug applications (ANDAs) or applications under section 505(b)(2) of the FDCA that reference or rely upon TRINTELLIX might seek to omit from their labeling important information regarding the relationship between vortioxetine and sexual dysfunction in an effort to avoid infringing a Lundbeck patent and circumvent statutory exclusivity.

The information protected by the relevant patent and exclusivity includes the only comparative data in the TRINTELLIX labeling regarding the drug's low association with sexual dysfunction in patients with major depressive disorder (MDD), relative to certain selective serotonin reuptake inhibitors (SSRIs). Before this information was added, the labeling reported TRINTELLIX's rates of voluntarily reported adverse reactions of sexual dysfunction in clinical trials as well as the rates of adverse sexual reactions as assessed by self-reported scores using the Arizona Sexual Experiences Scale (ASEX) in patients with normal sexual functioning at baseline. The newly added comparative information reports the results of a prospective study in patients experiencing SSRI-induced treatment-emergent sexual dysfunction (TESD) at baseline. In this study, improvement in TESD in patients switched to TRINTELLIX was superior to the improvement observed in patients who switched to escitalopram.

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Sexual dysfunction generally is associated with serotonergic antidepressants, a grouping of drugs that includes SSRIs, serotonin and norepinephrine reuptake inhibitors (SNRIs), and other drugs like TRINTELLIX. The protected information counters this conventional wisdom with respect to vortioxetine by informing prescribers that vortioxetine has a low association with sexual dysfunction in MDD patients, relative to certain SSRIs. It therefore increases prescribers' ability to select an appropriate antidepressant therapy, which mitigates the risk of potential non-adherence due to TESD. Additionally, this information better equips prescribers to evaluate and address any sexual dysfunction that may arise during vortioxetine therapy.

The safety and efficacy benefits resulting from the protected information are not limited to the protected condition of use; i.e., patients with a prior history of TESD from serotonin reuptake inhibitor treatment. As discussed below, the protected information increases safety and efficacy for patients who take TRINTELLIX regardless of whether they previously took another antidepressant or previously experienced TESD, and regardless of the reason for their switch (if any) from another antidepressant. Because a generic vortioxetine product would be less safe or effective than TRINTELLIX for the remaining, non-protected conditions of use, generic applicants should be required to include the protected information in their labeling.[1] The protected information also must be included in the labeling of vortioxetine products submitted in section 505(b)(2) applications for the labeling to comply with FDA's regulations regarding the Adverse Reactions and Clinical Studies sections of the prescribing information.[2]

A. Actions Requested

Takeda and Lundbeck respectfully request that the Commissioner require that the labeling for any drug product that is either (1) the subject of an abbreviated new drug application (ANDA) for which TRINTELLIX is the reference listed drug (RLD), or (2) a section 505(b)(2) application that relies upon TRINTELLIX, include the information from the TRINTELLIX labeling regarding the association between vortioxetine and sexual dysfunction that is identified in the appendix to this citizen petition.

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[1] *See* 21 C.F.R. § 314.127(a)(7); *see also id*. § 314.94(a)(8)(iv).

[2] *See* 21 C.F.R. § 201.57(c)(7) & (15).

B. Statement of Grounds

I. Background

A. Factual Background

1. TRINTELLIX

FDA approved TRINTELLIX tablets for the treatment of MDD in 2013.[3] TRINTELLIX is a novel antidepressant that acts as an inhibitor of the serotonin (5-hydroxytryptamine [5-HT]) transporter, as well as a 5-HT3, 5-HT7, and 5-HT1D receptor antagonist, a 5-HT1B receptor partial agonist, and a 5-HT1A receptor agonist.[4] TRINTELLIX's mechanism of action is not fully understood.[5]

TRINTELLIX was discovered by Lundbeck researchers in Denmark. The clinical trial program in the U.S. was conducted jointly by Lundbeck and Takeda. Takeda holds the TRINTELLIX NDA.

2. Major Depressive Disorder (MDD)

MDD—the condition that TRINTELLIX treats—is a complex mental health illness that may be associated with a range of emotional and physical symptoms. The diagnosis of MDD requires the presence of a "major depressive episode" that, among other criteria, involves either a depressed mood or loss of interest or pleasure in usual activities that persists over a period of at least two weeks and is accompanied by additional symptoms that may include significant weight loss or gain; insomnia or hypersomnia; psychomotor agitation or retardation; fatigue or

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[3] *See* FDA, Approval Letter, NDA 204447 (Sept. 30, 2013), https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2013/204447Orig1s000ltr.pdf (Exhibit 1). TRINTELLIX originally was approved under the proprietary name BRINTELLIX®. *See id*. In May 2016, FDA approved a change in the product's proprietary name 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 (Exhibit 2); *see also* FDA, Supplement Approval Letter, NDA 204477/S-007 (May 2, 2016) (Exhibit 3). To avoid confusion, this petition refers to the drug product as TRINTELLIX, including for the period of time when it was known as BRINTELLIX.

[4] TRINTELLIX Prescribing Information (PI) § 12.2 (Oct. 2018) (Exhibit 4).

[5] *Id*. § 12.1.

loss of energy; feelings of worthlessness or guilt; indecisiveness or diminished ability to think or concentrate; and recurrent thoughts of death or suicidal ideation.[6]

MDD is associated with high mortality, particularly due to suicide.[7] Depressive episodes may complicate other illnesses such as diabetes, morbid obesity, and cardiovascular disease.[8] MDD also can affect the patient's physical, social, and role functioning to varying degrees.[9]

Sexual dysfunction in both males and females may be part of depressive symptoms and/or may emerge as a sexual side effect of an antidepressant medication. These side effects appear to be more common with SSRIs.[10]

3. Information in the TRINTELLIX Labeling Regarding Sexual Dysfunction

a) Comparative Data Added to the TRINTELLIX Labeling in October 2018

FDA has recognized the value of assessing the relationship between antidepressants and sexual dysfunction and including this type of information in labeling. As early as the end-of-phase-2 meeting for TRINTELLIX in 2008, FDA advised that "if [Takeda] were able to show superiority to an active comparator (assuming the comparator were used in an optimal manner) and show non-inferiority to placebo for their drug, they may be able to add such findings to labeling."[11] In August 2012, FDA convened a Regulatory Science Forum to discuss methods of assessing and characterizing sexual dysfunction caused by antidepressant drugs.[12] Three years later, FDA authors published an article on this topic, noting that an antidepressant with fewer sexual side effects "if well documented, would in fact be an important clinical benefit."[13] Takeda and Lundbeck decided to conduct two clinical studies to assess the relationship between

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[6] American Psychiatric Association (APA), Diagnostic and Statistical Manual of Mental Disorders, DSM-5, at 160-61 (5th ed. 2013) (Exhibit 5).

[7] *Id*. at 164.

[8] *Id*. at 166.

[9] *Id*. at 167.

[10] APA, Practice Guideline for the Treatment of Patients with Major Depressive Disorder, at 36 (3d ed. 2010) (APA Practice Guideline) (Exhibit 6).

[11] FDA, Memorandum of Meeting Minutes, at 7 (meeting date Feb. 5, 2008; minutes dated Feb. 13, 2008), https://www.accessdata.fda.gov/drugsatfda_docs/nda/2013/204447Orig1s000AdminCorres.pdf (page 178/196) (emphasis added) (Exhibit 7).

[12] Khin NA, et al. *Regulatory and scientific issues in studies to evaluate sexual dysfunction in antidepressant drug trials*. J. Clin. Psychiatry. 2015 Aug;76(8):1060–3, at 1060 (Exhibit 8).

[13] *Id*. at 1061 (emphasis added).

vortioxetine and sexual dysfunction relative to certain SSRIs to provide the type of information that FDA has deemed important.

On October 19, 2018, FDA approved a supplemental NDA for TRINTELLIX that added to the labeling the results of the two randomized, double-blind, active-controlled studies that assessed sexual function using the Changes in Sexual Functioning Questionnaire Short Form (CSFQ-14). This instrument is a validated self-rated measure of sexual function for which a two to three-point change is considered clinically meaningful.[14] This recent labeling change added the first comparative data to be included in the TRINTELLIX labeling regarding the association between TRINTELLIX and sexual dysfunction relative to certain SSRIs.

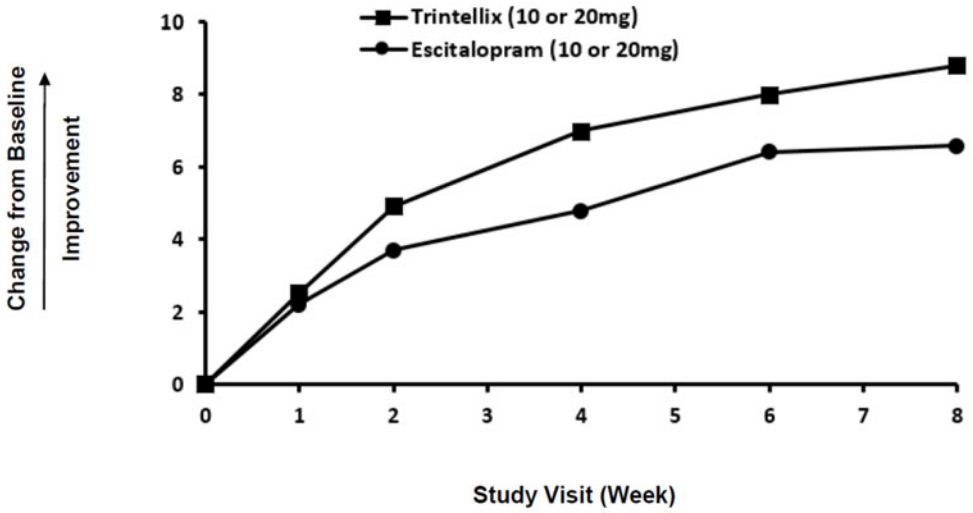
In the first study, patients who were taking citalopram, sertraline or paroxetine for at least eight weeks, whose depressive symptoms were adequately treated, and who were experiencing sexual dysfunction attributed to their SSRI treatment were switched to TRINTELLIX or escitalopram. For both TRINTELLIX and escitalopram, patients were started on 10 mg and increased to 20 mg at week 1, followed by flexible dosing. The Clinical Studies section of the labeling reports that:

> 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, while both drugs maintained the subject's prior antidepressant response. For change from Baseline in CSFQ-14, see *Figure 7*.[15]

[14] TRINTELLIX PI § 14 (Oct. 2018) (Exhibit 4).

[15] *Id*.

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



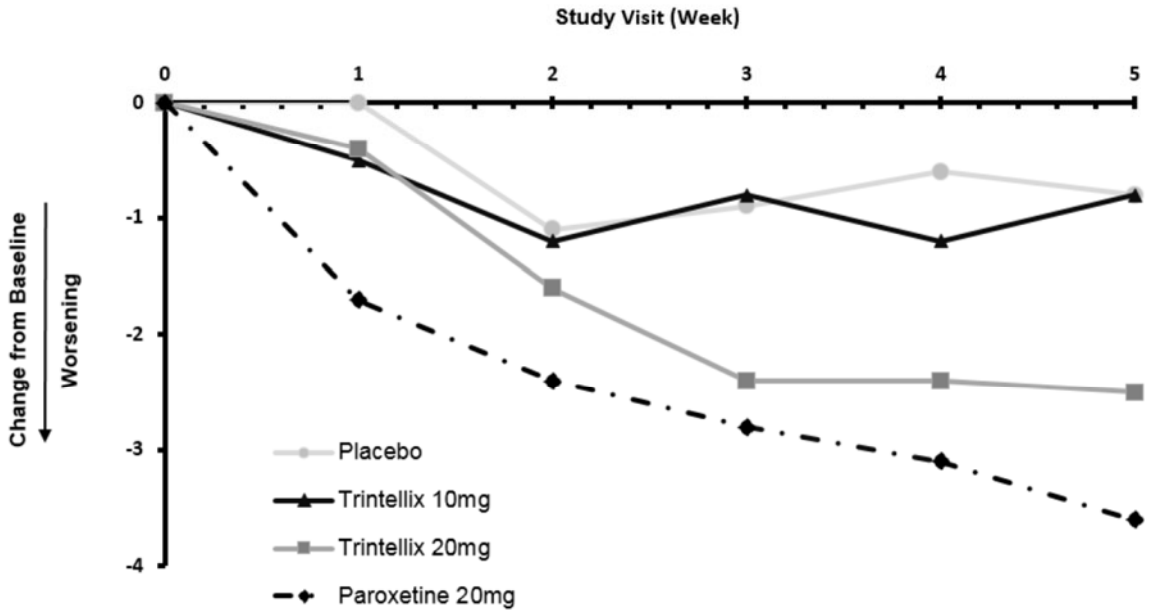
The quoted excerpt from TRINTELLIX's labeling reports the following two findings from the first study: (1) improvement in TESD in subjects switched to TRINTELLIX was superior as compared to escitalopram, and (2) subjects switched to either TRINTELLIX or escitalopram were able to maintain their prior antidepressant response after switching.

The second study was a five-week, randomized, double-blind, placebo- and paroxetine-controlled study conducted in 348 healthy volunteers with normal sexual functioning and without depression. The use of healthy volunteers in this study removed the confounding effect of depression. The Clinical Studies section of the labeling reports that:

> 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) *[see Adverse Reactions (6.1)]*. Paroxetine 20 mg was statistically significantly worse than placebo (n=89), confirming assay sensitivity in this study. For change from Baseline in CSFQ-14, see *Figure 8*.[16]

[16] *Id*.

Figure 8. Change from Baseline in CSFQ-14 Total Score by Study Visit (Week) in Healthy Volunteers (Study 11)



The information in the TRINTELLIX labeling relating to sexual dysfunction that is the subject of this petition appears in the appendix.

b) Information Previously Included in the TRINTELLIX Labeling Regarding Sexual Dysfunction

Before the recent addition of the comparative data described above, the TRINTELLIX labeling included certain non-comparative data regarding the association between TRINTELLIX and sexual dysfunction. Since the initial approval of TRINTELLIX, the Adverse Reactions section of the labeling has included the following information on voluntarily reported sexual adverse reactions in the six- to eight-week studies that established efficacy for MDD:

> In male patients the overall incidence was 3%, 4%, 4%, 5% in TRINTELLIX 5 mg/day, 10 mg/day, 15 mg/day, 20 mg/day, respectively, compared to 2% in placebo. In female patients, the overall incidence was <1%, 1%, <1%, 2% in TRINTELLIX 5 mg/day, 10 mg/day, 15 mg/day, 20 mg/day, respectively, compared to <1% in placebo.[17]

Also since initial approval, the TRINTELLIX labeling has stated that "[b]ecause voluntarily reported adverse sexual reactions are known to be underreported, in part because

[17] TRINTELLIX PI § 6.1 (Oct. 2018) (Exhibit 4); *see also* TRINTELLIX PI § 6.1 (Sept. 2013) (Exhibit 9).

patients and physicians may be reluctant to discuss them, the Arizona Sexual Experiences Scale (ASEX), a validated measure designed to identify sexual side effects, was used prospectively in seven placebo-controlled trials."[18] The labeling includes the following table showing the incidence of patients who developed TESD when treated with each of four fixed doses of TRINTELLIX or placebo:

Table 3. ASEX Incidence of Treatment Emergent Sexual Dysfunction*

	TRINTELLIX 5 mg/day N=65:67†	TRINTELLIX 10 mg/day N=94:86†	TRINTELLIX 15 mg/day N=57:67†	TRINTELLIX 20 mg/day N=67:59†	Placebo N=135:162†
Females	22%	23%	33%	34%	20%
Males	16%	20%	19%	29%	14%

* Incidence based on number of subjects with sexual dysfunction during the study/number of subjects without sexual dysfunction at baseline. Sexual dysfunction was defined as a subject scoring any of the following on the ASEX scale at two consecutive visits during the study: 1) total score ≥19; 2) any single item ≥5; 3) three or more items each with a score ≥4

† Sample size for each dose group is the number of patients (females:males) without sexual dysfunction at baseline

4. The '096 Patent

Lundbeck holds U.S. Patent No. 9,278,096 ('096 patent). The Orange Book reflects that information on the '096 patent was submitted for listing in connection with TRINTELLIX on November 13, 2018.[19] The use code for the '096 patent is "use in the treatment of major depressive disorder to improve Treatment Emergent Sexual Dysfunction (TESD) induced by prior serotonin reuptake inhibitor treatment."[20] As shown in the Orange Book, the current expiration date of the '096 patent is March 21, 2032.[21]

5. Three-Year Exclusivity

The information added to the TRINTELLIX labeling through the supplemental NDA that was approved on October 19, 2018 received three-year new clinical investigation exclusivity expiring on October 19, 2021.[22] The relevant exclusivity code is M-234, "update to the

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[18] TRINTELLIX PI § 6.1 (Oct. 2018) (Exhibit 4); *see also* TRINTELLIX PI § 6.1 (Sept. 2013) (Exhibit 9).

[19] FDA, Orange Book, https://www.accessdata.fda.gov/scripts/cder/ob/index.cfm (last visited Feb. 15, 2019) (patent and exclusivity information for TRINTELLIX) (Exhibit 10).

[20] *Id.*

[21] *Id.*

[22] *Id.*; *see* FDCA § 505(c)(3)(iv) & (j)(5)(F)(iv); 21 C.F.R. § 314.108(b)(5).

prescribing information for vortioxetine on treatment-emergent sexual dysfunction comparing vortioxetine and SSRIs."[23]

B. Legal and Regulatory Background

1. Patent Certifications and Section viii Statements

A new drug application (NDA) must include patent information for "any patent which claims the drug for which the applicant submitted the application or which claims a method of using such drug and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner engaged in the manufacture, use, or sale of the drug."[24] Within 30 days after approval of the NDA, the applicant again must submit patent information to FDA, including—in the case of a method-of-use patent—a "use code."[25] The use code is a brief description of the patented method of use that "must contain adequate information to assist 505(b)(2) and ANDA applicants in determining whether a listed method-of-use patent claims a use for which the 505(b)(2) or ANDA applicant is not seeking approval."[26] FDA publishes the patent information submitted by the NDA holder, including the use code, in the Orange Book.[27]

An ANDA or section 505(b)(2) application generally must include one of the following certifications concerning each patent for which the NDA holder is required to submit information to FDA:

> Paragraph I: the NDA holder has not filed patent information.
>
> Paragraph II: the patent has expired.
>
> Paragraph III: a statement of the date when the patent will expire.
>
> Paragraph IV: the patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the proposed follow-on product.[28]

Alternatively, the ANDA or section 505(b)(2) applicant may submit either a certification that there are no patents that are subject to listing by the NDA holder, or—most relevant here—a statement that a method-of-use patent does not claim an indication or other method of use for the proposed product because the applicant does not seek approval of a protected condition of

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[23] Orange Book, *supra* note 19 (Exhibit 10).

[24] FDCA § 505(b)(1).

[25] 21 C.F.R. § 314.53(c)(2)(ii)(P)(*3*).

[26] *Id*.

[27] *Id*. § 314.53(e).

[28] FDCA § 505(b)(2)(A) & (j)(2)(A)(vii); 21 C.F.R. §§ 314.50(i)(1)(i)(A) & 314.94(a)(12)(i)(A).

use.[29] The latter type of statement is known as a "section viii statement."[30] If the ANDA or section 505(b)(2) applicant submits a section viii statement, FDA will assess whether the "proposed carve-out label overlaps at all with the [RLD's] use code . . . . The FDA takes that code as a given: it does not independently assess the patent's scope or otherwise look behind the description authored by the [RLD holder] . . . . Only if the use code provides sufficient space for the generic's proposed label will the FDA approve an ANDA with a section viii statement."[31]

2. Labeling Carve-Outs

Generic drug labeling generally must have the same labeling as the RLD, among other statutory requirements for approval.[32] Differences in labeling are allowed if, under the exception relevant here, they result from the fact that "the new drug and the listed drug are produced or distributed by different manufacturers."[33] In a regulation, FDA has interpreted this exception to permit differences between the generic and RLD labeling where "aspects of the [RLD's] labeling are protected by patent, or by exclusivity, and such differences do not render the proposed drug product less safe or effective than the [RLD] for all remaining, non-protected conditions of use."[34] This standard determines whether FDA will approve an ANDA with labeling that omits—or "carves out"—information from the RLD's labeling that is protected by a patent or regulatory exclusivity.[35]

Although a section 505(b)(2) application is not subject to the "same labeling" requirement, the labeling for a section 505(b)(2) product—like all prescription drug labeling—must meet the requirements set forth in 21 C.F.R. §§ 201.57 and 201.100. For example, such labeling must "list the adverse reactions identified in clinical trials that occurred at or above a specified rate appropriate to the safety database" and, "[f]or adverse reactions with significant clinical implications, the listings must be supplemented with additional detail about the nature, frequency, and severity of the adverse reaction and the relationship of the adverse reaction to drug dose and demographic characteristics, if data are available and important."[36] Prescription drug labeling also "must discuss those clinical studies that facilitate an understanding of how to

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[29] FDCA § 505(b)(2)(B) & (j)(2)(A)(viii); 21 C.F.R. §§ 314.50(i)(1)(ii)-(iii) & 314.94(a)(12)(ii)-(iii).

[30] *Caraco Pharm. Labs., Ltd. v. Novo Nordisk A/S*, 566 U.S. 399, 406 (2012).

[31] *Id.* at 406-07.

[32] FDCA § 505(j)(2)(A)(v).

[33] *Id.*

[34] 21 C.F.R. § 314.127(a)(7) (emphasis added); *see also id.* § 314.94(a)(8)(iv).

[35] *See Bristol Myers Squibb Co. v. Shalala*, 91 F.3d 1493, 1500-01 (D.C. Cir. 1996) (upholding FDA's interpretation of the "different manufacturers" exception to allow carve-outs); *see also Sigma-Tau Pharms., Inc. v. Schwetz*, 288 F.3d 141, 148 n.3 (4th Cir. 2002) (upholding a carve-out of an indication protected by orphan-drug exclusivity).

[36] 21 C.F.R. § 201.57(c)(7)(ii)(A).

use the drug safely and effectively."[37]

II. Discussion

A. The labeling for generic vortioxetine products should be required to include certain comparative information from TRINTELLIX's labeling regarding sexual dysfunction.

1. The protected information describes vortioxetine's low association with sexual dysfunction relative to certain SSRIs.

Sexual dysfunction generally is understood to be associated with serotonergic antidepressants. For example, the American Psychiatric Association practice guideline describes sexual side effects as "appear[ing] to be more common with SSRIs."[38] Similarly, FDA observed during its review of the TRINTELLIX NDA that "[i]t is well known that SSRIs/SNRIs cause sexual dysfunction and the spontaneous report of sexual dysfunction related adverse events is under reported."[39]

The protected information distinguishes TRINTELLIX from certain SSRIs that are associated with TESD. As described in the background section above, the recent additions to the TRINTELLIX labeling report that the association between vortioxetine and sexual dysfunction is lower than that of certain SSRIs.[40] In particular, a study using the CSFQ-14 instrument found that patients with TESD induced by prior treatment with citalopram, sertraline, or paroxetine whose depressive symptoms were adequately treated at baseline experienced an improvement in TESD with TRINTELLIX, while the patients' prior antidepressant response was maintained.[41]

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[37] *Id*. § 201.57(c)(15).

[38] APA Practice Guideline, at 36 ("Although loss of erectile or ejaculatory function in men and loss of libido and anorgasmia in both sexes may be complications of virtually any antidepressant medication, these side effects appear to be more common with SSRIs.") (Exhibit 6); *see also* Cassano P, Fava M. *Tolerability issues during long-term treatment with antidepressants*. Ann Clin Psychiatry. 2004 Jan-Mar;16(1):15-25, at 17 ("Overall, SSRIs have been found to produce higher rates of sexual dysfunction . . . in the long-term as compared with the atypical antidepressants bupropion and nefazodone.") (Exhibit 11).

[39] FDA, Memorandum of Late-Cycle Meeting Minutes, at 6 (meeting date July 2, 2013; minutes dated Aug. 1, 2013), https://www.accessdata.fda.gov/drugsatfda_docs/nda/2013/204447Orig1s000AdminCorres.pdf (page 38/196) (Exhibit 12); *see also* Clinical Review, NDA 204447, at 112, https://www.accessdata.fda.gov/drugsatfda_docs/nda/2013/204447Orig1s000MedR.pdf (June 4, 2013) (TRINTELLIX Clinical Review) ("The use of psychotropic medications including SSRIs has been reported to cause sexual dysfunction (SD) during treatment of MDD.") (excerpts attached as Exhibit 13).

[40] *See* section B.I.A.3.a, *supra*.

[41] TRINTELLIX PI § 14, Fig. 7 (Oct. 2018) (Exhibit 4).

Patients who were switched to TRINTELLIX experienced a statistically significantly greater improvement in TESD than patients who were switched to escitalopram.[42] Because patients' depressive symptoms were adequately treated at baseline and antidepressant response was maintained after switching, the observed improvement in TESD can be attributed to TRINTELLIX's effect on sexual function, rather than the drug's effect on depressive symptoms.[43]

This study provides essential new information regarding the relationship between vortioxetine and sexual dysfunction that does not appear elsewhere in the TRINTELLIX labeling, including the only comparative data regarding the low association of sexual dysfunction with vortioxetine in MDD patients, relative to certain SSRIs. Moreover, the study provides essential context for the ASEX data that predate the addition of the new comparative data. Without the protected information, a prescriber viewing the ASEX data shown in Table 3 of the TRINTELLIX labeling might reach the incorrect conclusion that vortioxetine is associated with a high rate of sexual dysfunction because the incidence reported in Table 3 ranges from 16 percent to 34 percent.[44] Although the rate of sexual dysfunction also is relatively high for placebo (14 percent in males and 20 percent in females), the prescriber might not take that fact into consideration. Nor does Table 3 enable a prescriber to place the ASEX data in context because, to our knowledge, only one other antidepressant, CYMBALTA® (duloxetine), includes ASEX data in its labeling, and those data are reported differently; i.e., mean change in ASEX score rather than TESD incidence.[45]

The protected information thus enables the prescriber to correctly understand that TRINTELLIX in fact has a low incidence of sexual dysfunction relative to certain SSRIs, notwithstanding what may appear to be a high incidence of TESD reported in Table 3. The protected labeling functions as a corrective lens that prevents the prescriber from being misled by the ASEX data 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.

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[42] *Id*. § 14. Patients who were switched to escitalopram nonetheless experienced improvement in TESD.

[43] *Id*.

[44] TRINTELLIX PI § 6.1 (Oct. 2018) (Exhibit 4). Table 3 is reprinted in section B.I.A.3.b, *supra*.

[45] *See* CYMBALTA PI § 6.6 (Dec. 2017) (Exhibit 14).

2. The omission of the protected information would make a generic vortioxetine product less safe or effective than TRINTELLIX for the remaining, non-protected conditions of use.

The protected information about the low association between vortioxetine and sexual dysfunction in MDD patients, relative to certain SSRIs, improves prescribers' ability to make decisions that increase safety and efficacy at two distinct time points: first, when a prescriber initially selects a therapy for a given patient; and second, when any sexual dysfunction occurs during treatment of a patient on vortioxetine.

At the first time point—when selecting an antidepressant—the protected information about the low association between vortioxetine and sexual dysfunction in MDD patients relative to other SSRIs improves the prescriber's ability to make appropriate clinical treatment decisions in the patient's best interest for efficacy and safety and to increase the likelihood of treatment adherence. Sexual dysfunction is among the side effects deemed most bothersome to patients taking antidepressants.[46] If sexual dysfunction occurs during therapy, it can lead to treatment non-adherence.[47] A patient who stops taking an effective therapy due to sexual dysfunction could experience relapse and greater risk associated with untreated MDD symptoms.[48]

Without the protected information in TRINTELLIX's labeling about the low association between vortioxetine and sexual dysfunction in MDD patients relative to certain SSRIs, the labeling would not include any comparative data regarding vortioxetine's association with sexual dysfunction in MDD patients.[49] Accordingly, the prescriber might assume that the association between vortioxetine and sexual dysfunction is stronger than it really is, based upon the conventional wisdom about serotonergic antidepressants, the prescriber's experience with such

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[46] Hu XH, et al. *Incidence and duration of side effects and those rated as bothersome with selective serotonin reuptake inhibitor treatment for depression: patient report versus physician estimate.* J Clin Psychiatry 2004. Jul;65(7):959-65, at 963 ("Among the side effects studied, drowsiness and sexual dysfunction appeared to be the most problematic for patients. These side effects were experienced by over one third of the patients, and nearly half of them felt that these side effects were 'a lot' or 'extremely' bothersome.") (Exhibit 15).

[47] Clayton AH, et al. *Prevalence of sexual dysfunction among newer antidepressants.* J Clin Psychiatry. 2002 Apr;63(4):357-66, at 358 ("[S]exual dysfunction is a common cause of noncompliance with antidepressant treatment regiments, which can lead to relapse of depression.") (Exhibit 16).

[48] Cassano, *supra* note 38, at 16 ("Long-term side effects are a challenge to effective therapy because they diminish quality of life, which depends not only on the resolution of residual symptoms or on the occurrence of depressive breakthroughs, but also on drug tolerability . . . Furthermore, high rates of non-adherence have been associated with reduced antidepressant efficacy.") (Exhibit 11).

[49] Before the protected comparative data were added, the TRINTELLIX labeling contained information about voluntarily reported sexual adverse reactions and the incidence of sexual dysfunction relative to placebo. *See* section B.I.A.3.b, *supra*.

medicines, or a misinterpretation of the ASEX data reported in Table 3.[50] This incorrect assumption might lead the prescriber not to consider vortioxetine for a patient who could experience greater tolerability and treatment adherence with vortioxetine due to its low association with sexual dysfunction relative to certain SSRIs. The protected information overcomes such preconceptions by providing accurate comparative data about vortioxetine in MDD patients. With this information, the prescriber is more likely to consider vortioxetine for a given patient because it may increase the likelihood of the patient's treatment adherence, thereby enhancing efficacy and safety for the patient.[51]

Importantly, the protected information about the low association between vortioxetine and sexual dysfunction in MDD patients (relative to certain SSRIs) enables prescribers to increase the likelihood of treatment adherence for patients beyond the protected condition of use, such as patients who did not previously experience TESD or take a serotonin reuptake inhibitor, or patients who switched from another antidepressant for a reason other than TESD. The patient, regardless of his or her history, might consider sexual dysfunction to be sufficiently bothersome that it would cause him or her to stop taking an antidepressant if it were to occur during therapy. Accordingly, omitting the protected information would cause a generic product to be less safe or effective than TRINTELLIX for the non-protected conditions of use by increasing the risk that the prescriber would not consider vortioxetine as a treatment option in patients for whom it could improve treatment adherence.[52] Making this information available to prescribers for all patients would increase safety and effectiveness because it is not possible to determine in advance, with certainty, whether any particular patient might experience sexual side effects that would cause the patient to stop taking the drug.

At the second time point—when sexual dysfunction, if any, occurs during vortioxetine therapy—the prescriber needs access to the protected information about the low association of vortioxetine and sexual dysfunction (relative to certain SSRIs) in order appropriately to manage treatment without compromising safety or efficacy. Here, too, omitting the protected

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[50] *See* section B.II.A.1, *supra*.

[51] *See* Cassano, *supra* note 38, at 16 ("It is . . . essential for clinicians to be familiar with the tolerability profile of antidepressants" because "[t]olerability issues may affect the physician's decision to initiate antidepressant treatment among particular patient populations. . . [or] to lengthen antidepressant treatment in the continuation and maintenance phases."); *id*. at 18 ("[T]he relative risk of short- and long-term side effects should inform the selection of an antidepressant drug . . . [E]ducation [of patients] alone most likely will not improve long-term treatment adherence in the face of antidepressant-induced side effects, as demonstrated in a large study conducted in primary care.") (Exhibit 11); Bostwick JM. *A generalist's guide to treating patients with depression with an emphasis on using side effects to tailor antidepressant therapy*. Mayo Clin Proc. 2010 Jun;85(6):538-50, at 541 ("Knowing that all [antidepressants (ADs)] have similar efficacy, the generalist faced with choosing an appropriate AD would do well to base rational treatment decisions on differences in side effects among the available ADs . . . . Aggressive side-effect management can improve adherence, enhance comfort and function, and obviate premature discontinuation.") (Exhibit 17).

[52] *See* 21 C.F.R. § 314.127(a)(7).

information might cause the prescriber to assume incorrectly that the association between vortioxetine and sexual dysfunction is stronger than it is, based upon commonly held beliefs about serotonergic antidepressants, experience treating patients using such drugs, or a misunderstanding of the ASEX data reported in Table 3.[53] This incorrect assumption might lead the prescriber to attribute any sexual dysfunction occurring during vortioxetine therapy to the drug even if there is some other cause.[54] Moreover, the protected information enables the prescriber to counsel the patient appropriately that any sexual dysfunction occurring during treatment is more likely to be a symptom of MDD or result from some other cause rather than an adverse reaction associated with vortioxetine. There is a significant likelihood that sexual dysfunction improperly might be attributed to vortioxetine rather than another cause: as noted, in seven placebo-controlled studies using the ASEX scale, 14 percent of males and 20 percent of females taking a placebo reported TESD. [55]

Without the protected information, the occurrence of sexual dysfunction might prompt the prescriber to switch the patient to another antidepressant or other therapy, even if the drug is effective in treating the patient's depression.[56] Alternatively, non-adherence to treatment might occur if the prescriber has not advised the patient that any sexual dysfunction occurring with vortioxetine is unlikely to be caused by the drug. Such non-adherence to treatment or switch of a stable patient to another antidepressant or other therapy may disrupt therapy with the potential for efficacy and safety issues after drug therapy ends or during the transition period following any medication change. In the case of a switch to another antidepressant, there may be a period when "the benefits of the discontinued medication are fading while the new medication has not yet exerted significant clinical effects."[57] Although the labeling notes that TRINTELLIX can be discontinued abruptly,[58] the prescriber might seek to minimize withdrawal symptoms and the risk of relapse by using a "cross-taper strategy, where the first antidepressant dose is reduced while the second antidepressant is introduced at a low dose and gradually increased."[59] Such an approach "can be done safely with only some antidepressants," requires

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[53] *See* section B.II.A.1, *supra*.

[54] *See* APA Practice Guideline, at 36 ("The psychiatrist should ascertain whether the reported sexual dysfunction is a result of the antidepressant medication, the underlying [MDD], a co-occurring medical disorder, a disturbance in a relationship, or a need for education about sexual functioning.") (Exhibit 6).

[55] See section B.I.A.3.b. *supra*.

[56] *See* APA Practice Guideline, at 36, 38 ("If sexual dysfunction is determined to be a side effect of the antidepressant medication, a number of strategies are available, including continuing treatment to assess whether the dysfunction will disappear with time, lowering the dose, discontinuing the antidepressant, or substituting another antidepressant such as bupropion.") (Exhibit 6).

[57] Cassano, *supra* note 38, at 18 (Exhibit 11).

[58] TRINTELLIX PI § 2.3 (Oct. 2018) (Exhibit 4).

[59] Keks N et al. *Switching and stopping antidepressants*. Aust Prescr. 2016 Jun;39(3):76-83 (Exhibit 18); *see also* Ogle NR, Akkerman SR. *Guidance for the discontinuation or switching of antidepressant therapies in adults*. J Pharm Pract. 2013 Aug;26(4):389-96, at 390 ("During

"considerable expertise," and introduces uncertainty into the treatment of a patient who is stable and responding to treatment.[60]

In this context, too, the protected information increases the safety and effectiveness of vortioxetine for a broader set of patients than those taking the drug for the protected condition of use. Patients might experience sexual dysfunction while taking vortioxetine regardless of whether they previously took a serotonin reuptake inhibitor or experienced TESD, and regardless of the reason for their switch (if any) from another antidepressant. Accordingly, patients other than those in the protected condition of use might experience the outcomes described above if sexual dysfunction occurs during vortioxetine therapy: they might be switched to another antidepressant due to the prescriber's incomplete or erroneous understanding of the low association between vortioxetine and sexual dysfunction relative to certain SSRIs, or might stop treatment due to a lack of guidance from the prescriber on that low association.

Including this information in labeling for all patients increases safety and effectiveness because it is not possible to identify in advance which patients will experience sexual dysfunction that triggers treatment cessation or a switch to another antidepressant. By increasing the likelihood of treatment cessation or a drug switch for MDD patients—with the attendant risk of safety and efficacy issues following treatment termination or during the transition to another therapy—the omission of the protected information would cause a generic vortioxetine product to be less safe or effective than TRINTELLIX for the remaining, non-protected conditions of use.[61]

3. Requiring generic labeling to include the protected information would be consistent with FDA's precedents.

Requiring generic labeling to include the protected information about the low association of vortioxetine with sexual dysfunction, relative to certain SSRIs, would be consistent with FDA's precedents. For example, in 2004, FDA determined that ANDAs referencing Rapamune® (sirolimus) could not omit certain information from their labeling. Rapamune is an immunosuppressive agent that was approved for the prophylaxis of organ rejection in patients receiving renal transplants.[62] Rapamune originally was approved only for use in combination with cyclosporine and corticosteroids, but the use in combination with cyclosporine later was found to be associated with increased renal function impairment.[63] Based on a clinical study that was conducted in patients at low to moderate risk of immune system

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tapering or cross tapering of any medication, it is important to monitor tolerability and adjust dosing according to individual patient reactions.") (Exhibit 19).

[60] Keks, *supra* note 59, at 78 (Exhibit 18).

[61] 21 C.F.R. § 314.127(a)(7).

[62] Letter from Steven K. Galson, M.D., M.P.H., FDA, to Michael S. Labson & Elizabeth M. Walsh, Covington & Burling, re: Docket No. 2003P-0518/CP1, at 1 (Sept. 20, 2004) (Exhibit 20).

[63] *Id*.

reactions, FDA approved labeling for Rapamune regarding cyclosporine withdrawal procedures in low-to-moderate-risk patients.[64] This labeling received three-year exclusivity.[65]

FDA concluded that omitting the protected information would make a generic sirolimus product less safe or effective than Rapamune for the non-protected conditions of use because "the protected labeling . . . contains extensive, critical prescribing information pertaining to cyclosporine withdrawal that any physician should receive to appropriately determine treatment for all indications for sirolimus."[66] Among other things, FDA determined that information about the "cyclosporine-sparing regimen" was necessary for the non-protected condition of use—i.e., the high-risk population—because a high-risk patient might later be reclassified as a low- to moderate-risk patient "and conceivably could benefit from a cyclosporine-sparing regimen."[67] FDA also found that "information on such a regimen is necessary for prescribing physicians to titrate or individualize the graft recipient's immunosuppressive therapy."[68]

Similarly, FDA determined that the labeling of any generic colchicine product referencing Colcrys® (colchicine) and seeking approval for prophylaxis of gout flares could not carve out the RLD's protected dosing regimen for the treatment of acute gout flares.[69] FDA reasoned that a patient taking colchicine for prophylaxis later might need the drug to treat an acute gout flare. If so, information about the protected dosing regimen, including the maximum recommended dose for the treatment of acute gout flares, would be important to minimize the risk of cumulative toxicity.[70]

In both of these precedents, FDA reasoned that a carve-out was impermissible because the condition of a patient initially taking the drug for a non-protected condition of use later might change in a way that would make the protected information relevant to the safe use of the product by that patient. The same reasoning compels the denial of a carve-out of the protected information at issue here. Just as a high-risk transplant patient later might be reclassified as a low- to moderate-risk patient who "conceivably could benefit" from information about the cyclosporine withdrawal regimen for Rapamune, and just as a patient taking Colcrys for prophylaxis of gout flares later might experience an acute gout flare and need information about the maximum recommended dose for the treatment indication, so too might a patient taking vortioxetine for the non-protected condition of use (i.e., without TESD induced by prior serotonin reuptake inhibitor treatment) later experience sexual dysfunction during treatment. In light of that possibility, the patient "conceivably could benefit" from the information regarding the low association of vortioxetine with sexual dysfunction relative to certain SSRIs

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[64] *Id*.

[65] *Id*. at 1-2.

[66] *Id*. at 3.

[67] *Id*. at 4.

[68] *Id*.

[69] *See* Letter from Janet Woodcock, M.D., FDA, to Gary L. Veron, Esq., Sidley Austin LLP, re: Docket No. FDA-2010-P-0614, at 24, 27 (May 25, 2011) (Exhibit 21).

[70] *Id*. at 24.

because this information enables the prescriber to select an antidepressant that the patient is most likely to keep taking and to appropriately manage any sexual dysfunction that occurs during vortioxetine therapy. Because the prescriber cannot determine in advance the specific patients for whom this information will be necessary, making the information available for the general MDD population increases safety and effectiveness.

Consistent with FDA's precedents, and for the reasons discussed above, omitting the protected sexual dysfunction information from generic labeling would render a generic vortioxetine product less safe or effective than TRINTELLIX for the remaining, non-protected conditions of use, and indeed is essential for the safety and effectiveness of a generic product. Accordingly, the protected information cannot be excluded from the labeling of a generic vortioxetine product.[71]

B. The labeling for section 505(b)(2) products should be required to include the same comparative information from TRINTELLIX's labeling regarding sexual dysfunction.

Although a section 505(b)(2) application is not subject to a "same labeling" requirement, FDA should require the labeling for a section 505(b)(2) product that relies upon TRINTELLIX to include the protected information from the TRINTELLIX labeling regarding the low association of vortioxetine and sexual dysfunction, relative to certain SSRIs. This information needs to be included in the section 505(b)(2) labeling for it to comply with the general prescription drug labeling regulations—in particular, 21 C.F.R. §§ 201.57 and 201.100.

First, section 201.57 of FDA's regulations requires, in relevant part, that the labeling "list the adverse reactions identified in clinical trials that occurred at or above a specified rate appropriate to the safety database" and, "[f]or adverse reactions with significant clinical implications, the listings must be supplemented with additional detail about the nature, frequency, and severity of the adverse reaction and the relationship of the adverse reaction to

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[71] *See* 21 C.F.R. § 314.127(a)(7). The express language of the regulation does not require that the omission of the protected information would render the generic drug product unsafe or ineffective for the remaining, non-protected conditions of use in order for FDA to deny a carve-out. Rather, the regulation allows a carve-out to be denied even if the drug product would remain safe and effective without the protected information, as long as the omission would make the drug less safe or effective than the RLD for the remaining, non-protected conditions of use. By focusing on the relative safety and efficacy of the generic product and RLD, the regulation helps ensure that the generic product and RLD "can be expected to have the same clinical effect and safety profile when administered to patients under the conditions specified in the labeling." 21 C.F.R. § 314.3(b) (definition of "therapeutic equivalents"). We note that FDA recently described the standard in terms that are difficult to reconcile with the language of the regulation. *See, e.g.,* Letter from Janet Woodcock, M.D., to Richard L. Gulino, Vanda Pharmaceuticals Inc., re: Docket No. FDA-2016-P-2654, at 6 (Nov. 28, 2016) (stating that ANDA applicants may carve out protected conditions of use "as long as the ANDA remains safe and effective for the remaining non-protected conditions of use.") (Exhibit 22).

drug dose and demographic characteristics, if data are available and important."[72] It cannot reasonably be disputed that sexual dysfunction meets the relevant definition of "adverse reaction" in connection with vortioxetine, given that it is included in the Adverse Reactions section of the TRINTELLIX labeling.[73]

FDA's regulations require the specific information in the TRINTELLIX labeling about sexual dysfunction to be included in the labeling for a section 505(b)(2) product because this adverse reaction can have "significant clinical implications," including with respect to treatment adherence, and this information provides "available and important" data containing "additional detail about the nature, frequency, and severity of the adverse reaction and the relationship of the adverse reaction to drug dose and demographic characteristics."[74] As noted, the protected information constitutes the first comparative data in the TRINTELLIX labeling regarding sexual dysfunction in MDD patients. Accordingly, section 201.57 would require section 505(b)(2) labeling to include the protected information describing the low association between vortioxetine and sexual dysfunction in MDD patients, relative to certain SSRIs.

Second, section 201.100 of FDA's regulations requires that prescription drug labeling "discuss those clinical studies that facilitate an understanding of how to use the drug safely and effectively."[75] Generally, this includes "those studies that were essential to establishing the drug's effectiveness for the purpose of obtaining marketing approval."[76] FDA explains in guidance that applicants ordinarily should include more detail regarding a study in some

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[72] 21 C.F.R. § 201.57(c)(7)(ii)(A).

[73] An "adverse reaction" means "an undesirable effect, reasonably associated with the use of a drug, that may occur as part of the pharmacological action of the drug or may be unpredictable in its occurrence. 21 C.F.R. § 201.57(c)(7). This definition does not include all adverse events observed during use of a drug, but is instead limited to "only those adverse events for which there is some basis to believe there is a causal relationship between the drug and the occurrence of the adverse event." *Id*. FDA explains in guidance that "[d]ecisions on whether there is some basis to believe there is a causal relationship are a matter of judgment and are based on factors such as . . . whether the adverse event is known to be caused by related drugs." FDA, Guidance for Industry, *Adverse Reactions Section of Labeling for Human Prescription Drug and Biological Products—Content and Format*, at 8 (Jan. 2006). In the clinical review for the TRINTELLIX NDA, FDA identified sexual dysfunction as among the "Significant [Adverse Events (AEs)]/AEs of Special Interest." TRINTELLIX Clinical Review, at 72 (excerpts attached as Exhibit 13).

[74] 21 C.F.R. § 201.57(c)(7)(ii)(A).

[75] 21 C.F.R. § 201.57(c)(15).

[76] 71 Fed. Reg. 3922, 3953 (Jan. 24, 2006).

situations, such as when "[t]he study results are not what would be expected for that drug class and indication."[77]

The clinical study information in the TRINTELLIX labeling regarding the comparative study assessing sexual dysfunction in MDD patients, relative to certain SSRIs, must be included in section 505(b)(2) labeling because it "facilitate[s] an understanding of how to use [the] drug safely and effectively" for the reasons discussed above.[78] Moreover, given the generally understood relationship between serotonergic antidepressants and sexual dysfunction, the results reported in the protected labeling "are not what would be expected for that drug class and indication," further supporting their inclusion in the labeling of a section 505(b)(2) product.[79] For these reasons, a section 505(b)(2) product referencing TRINTELLIX should be required to include in its labeling the protected information regarding the low association between vortioxetine and sexual dysfunction in MDD patients, relative to certain SSRIs.

III. Conclusion

For the foregoing reasons, FDA should require that the labeling for drug products referencing or relying upon TRINTELLIX include the information from the TRINTELLIX labeling regarding the association between vortioxetine and sexual dysfunction in MDD patients, relative to certain SSRIs, that is identified in the appendix to this citizen petition.

C. Environmental Impact

The actions requested herein are subject to categorical exclusion under 21 C.F.R. §§ 25.30 and 25.31.

D. Economic Impact

Pursuant to 21 C.F.R. § 10.30(b), an economic impact statement will be submitted only upon the request of the Commissioner.

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[77] FDA, Guidance for Industry, *Clinical Studies Section of Labeling for Human Prescription Drug and Biological Products—Content and Format*, at 4 (Jan. 2006) (Clinical Studies Labeling Guidance).

[78] 21 C.F.R. § 201.57(c)(15); *see* section B.II.A,2, *supra*.

[79] Clinical Studies Labeling Guidance, at 4.

E. Certification

I certify that, to my best knowledge and belief: (a) this petition includes all information and views upon which the petition relies; (b) this petition includes representative data and/or information known to the petitioner which are unfavorable to the petition; and (c) I have taken reasonable steps to ensure that any representative data and/or information which are unfavorable to the petition were disclosed to me. I further certify that the information upon which I have based the action requested herein first became known to the party on whose behalf this petition is submitted on or about the following date: November 13, 2018, the submission date for information regarding U.S. Patent No. 9,278,096; and October 19, 2018, the date of approval of NDA 204447/S-017, which added to the TRINTELLIX labeling information regarding the association between vortioxetine and sexual dysfunction relative to certain SSRIs. If I received or expect to receive payments, including cash and other forms of consideration, to file this information or its contents, I received or expect to receive those payments from the following persons or organizations: I am making these representations on behalf of Takeda or Lundbeck as part of my responsibilities as an employee of Takeda or Lundbeck; I am not being separately compensated for submitting this petition. I verify under penalty of perjury that the foregoing is true and correct as of the date of the submission of this petition.

Respectfully submitted,

Jin Chon
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Global Program Leader, CNS Medical
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Doug Williamson
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Lundbeck

Appendix

Information in the TRINTELLIX Labeling Regarding the Association between TRINTELLIX and Sexual Dysfunction in MDD Patients Relative to Certain SSRIs

6 ADVERSE REACTIONS

6.1 Clinical Studies Experience

Sexual Dysfunction
In addition to the data from the 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, while 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