CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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OFFICE DIRECTOR MEMO

Deputy Office Director Decisional Memo

Date	(electronic stamp)
From	Robert Temple, MD
Subject	Deputy Office Director Decisional Memo
NDA/BLA # **Supplement #**	204447
Applicant Name	Takeda Pharmaceuticals USA, Inc.
Date of Submission	October 2, 2012
PDUFA Goal Date	October 2, 2013
Proprietary Name / **Established (USAN) Name**	Brintellix/(vortioxetine)
Dosage Forms / Strength	Immediate Release Tablets/5 mg, 10 mg, 15 mg and 20 mg
Proposed Indication(s)	Major Depressive Disorder
Action:	Approval

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Medical Officer Review	Jenn Sellers, MD, PhD
Statistical Review	George Kordzakhia, PhD
Pharmacology Toxicology Review	Antonia Dow, PhD
CMC Review/OBP Review	Wendy Wilson-Lee, PhD Houda Mahayni, PhD
Microbiology Review	
Clinical Pharmacology Review	Andre Jackson, PhD Li Zhang, PhD
OPDP	Susannah O'Donnell, MPH
OSI	Sripal R. Mada, PhD John Lee, MD
CDTL Review	Jing Zhang, MD
OSE/DEpi	Cary Parker
OSE/DMEPA	Loretta Holmes, PharmD
OSE/DRISK	Reema Mehta
Other – Div Dir Review Dep Dir for Safety Review	Mitchell Mathis, MD

OND=Office of New Drugs
OPDP=Office of Prescription Drug Promotion
OSI=Office of Scientific Investigations
CDTL=Cross-Discipline Team Leader
OSE= Office of Surveillance and Epidemiology
DEPi= Division of Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DRISK=Division of Risk Management

I. Introduction

Vortioxetine is an antidepressant with one established mechanism (selective inhibition of serotonin reuptake, SSRI) and other potential mechanisms, affecting various serotonin receptors and transporters, whose contribution to the antidepressant effect is uncertain. A total of 10 short-term (6-8 weeks) studies in acute depression, 5 conducted entirely in the United States, were carried out, together with one relapse-prevention study conducted outside the United States (OUS). Almost all studies randomized patients to > 1 dose (most 5, 10, 15, or 20 mg) and higher doses were invariably more effective. Although the 5 mg dose appeared effective in the OUS trials, it consistently failed to show an effect in US studies, a major consideration in dosing recommendations. In US trials, the 20 mg dose had a clearly greater effect than 10 or 15 mg. A starting dose lower than 20 mg is recommended because this reduces the frequency of nausea, the drug's most troublesome common adverse effect and the most common reason for drug discontinuation. Nausea decreases in frequency over time.

Vortioxetine is about 75% bioavailable and metabolized largely by cytochrome p 450 2D6, followed by glucuronidation. Its half-life is quite long, about 66 hours, so that steady state is reached in about 2 weeks (4 half lives would be about 11 days). Strong P450 2D6 inhibitors increase AUC and C_{max} by about 2.3-fold, but other inhibitors (3A4, 2C19) have little effect. Strong 2D6 inducers like rifampin reduce blood levels by about 50%. Vortioxetine did not have a significant effect on the QTc interval or on driving performance.

Chemistry and toxicology issues did not present problems and are discussed in the in the Division Director and CDTL reviews of Drs. Mathis and Zhang, as well as the chemistry, toxicology, and Biopharmaceutics reviews.

II. Effectiveness

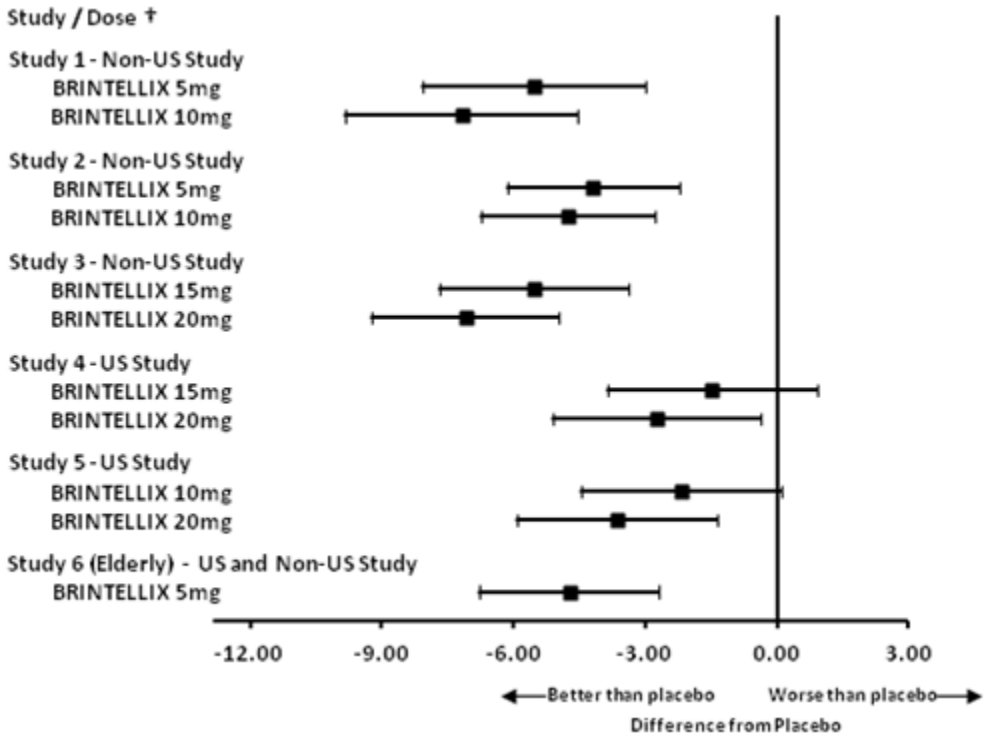
Vortioxetine was studied in 10 placebo-controlled trials in patients with a major depressive episode. All were 6-8 weeks and all used either a MADRS or HAMD-24 endpoint, with either a mixed model repeated measures (MMRM) or last-observation carried forward (LOCF) analysis to account for missing data. One study was conducted in patients ages 64 to 88 years. There was, in addition, a maintenance study of people with a history of major depression who were in remission on vortioxetine 5 mg or 10 mg at the start of the double-blind period of the study. The features and results of the 10 short-term studies are shown in Table 1; data are obtained from the reviews of Drs. Sellers and Kordzakhia. Total sample sizes for each study (omitting some who received lower doses) are shown, all studies used 1:1 randomization. The difference between US and OUS studies is fairly striking, with consistently larger effects outside the US and little hint of an effect of 5 mg in the US in 2 good sized studies, one of which showed unequivocal assay sensitivity using a duloxetine group.

The successful US and OUS studies are shown in figure 5 of labeling (reproduced below). The Studies 1, 2, and 3 are Studies 11492A, 305, and 13267A, respectively; 4 and 5 are US Studies 315 and 316, respectively.

Table 1

	Study No, region, endpoint (inclusion)	Drug dose groups	Baseline	Change from Base	Plbo-subtracted	P value
1	11492A Eur, Aust, Can MADRS, ≥ 30 Total n =425	5 mg 10 mg Ven 225 placebo	34.1 34.0 34.2 33.9	-20.4 -20.2 -20.9 -14.5	-5.9 -5.7 -6.4 --	< 0.001 < 0.001 < 0.001 --
2	305 En, As, Aus, S. Af MADRS ≥ 26 Total n = 419	5 mg 10 mg placebo	32.3 33.1 32.7	-15.4 -16.2 -11.3	-4.1 -4.9 -- --	< 0.001 < 0.001 --
3	13267A Eu, S. Af MADRS ≥ 26 Total n =608	15 mg 20 mg dulox 60 placebo	31.8 31.2 31.2 31.5	-17.2 -18.8 -21.2 -11.7	-5.5 -7.1 -9.5 --	< 0.001 < 0.001 < 0.001 --
4	315 US MADRS ≥ 26 Total n =591	15 mg 20 mg Dulox 60 placebo	31.9 32.0 32.8 31.5	-14.3 -15.6 -16.9 -12.8	-1.5 -2.8 -4.1 --	0.224 0.023 <0.001 --
5	316 US MADRS ≥ 26 Total n = 457	10 mg 20 mg placebo	32.3 32.4 32.0	-13.0 -14.4 -10.8	-2.2 -3.6 -- --	0.058 (pos at week 6) 0.002 --
6	12541 (elderly) Eu, Can, US MADRS ≥ 26 Total n =453	5 mg Dulox 60 placebo	29.2 28.5 29.4	-13.7 -15.8 -10.3	-3.3 -5.5 --	<0.001 < 0.001 --
7	11984A Eur, Can, As, Aust MADRS ≥ 26 Total n =600	5 mg 10 mg Dulox 60 placebo	32.7 31.8 31.4 31.7	-16.5 -16.3 -16.8 -14.8	-1.7 -1.5 -2.0 --	0.132 0.185 0.074 --
8	317 US MADRS≥ 26 Total n = 434	10 mg 15 mg placebo	34.2 33.9 33.5	-13.7 -13.4 -12.9	-0.8 -0.5 --	0.597 0.745 --
9	303 US MADRS≥ 30 Total n = 578	5 mg placebo	32.7 32.1	-14.6 -13.9	-0.7 --	0.407 --
10	304 US MADRS≥ 22 Total n = 451	5 mg Dulox 60 placebo	29.8 28.8 29.5	-11.1 -13.5 -10.5	-0.6 -3.0 --	0.577 0.005 --

Figure 5. Difference from Placebo in Mean Change from Baseline in MADRS Total Score at Week 6 or Week 8



It is noteworthy that, directionally at least, the larger doses were always more effective and that effect sizes were substantially greater outside the US. With 2 failed US studies at 5 mg, and a considerably smaller effect in the US patients in Study 12541 (elderly) we concluded there was no good reason to use the 5 mg dose. The 10 mg dose was actually effective at Week 6 in Study 316. Labeling therefore recommends starting with 10 mg (20 mg would give undesirable levels of nausea) and going to 20 mg if tolerated, which was the method used in trials that gave 15-20 mg. There were extensive discussions with the sponsor, who preferred leaving dose to the clinician's judgment. We felt that the long half-life and relatively slow onset of effect (typical of many anti-depressants), and the modest drug-placebo difference made an informed judgment of success difficult at best and concluded that the best advice was to give 20 mg and back down if necessary.

The true course of effect on MADRS is shown below for US Studies 315 and 316 (lines labeled Lu are vortioxetine). Effects at 2 weeks are modest and would be quite difficult to detect. This modest 2 week effect was also seen in the OUS studies).

Figure 3: Change From Baseline in MADRS Total Score by Week (FAS, MMRM) - Study 315 (US)

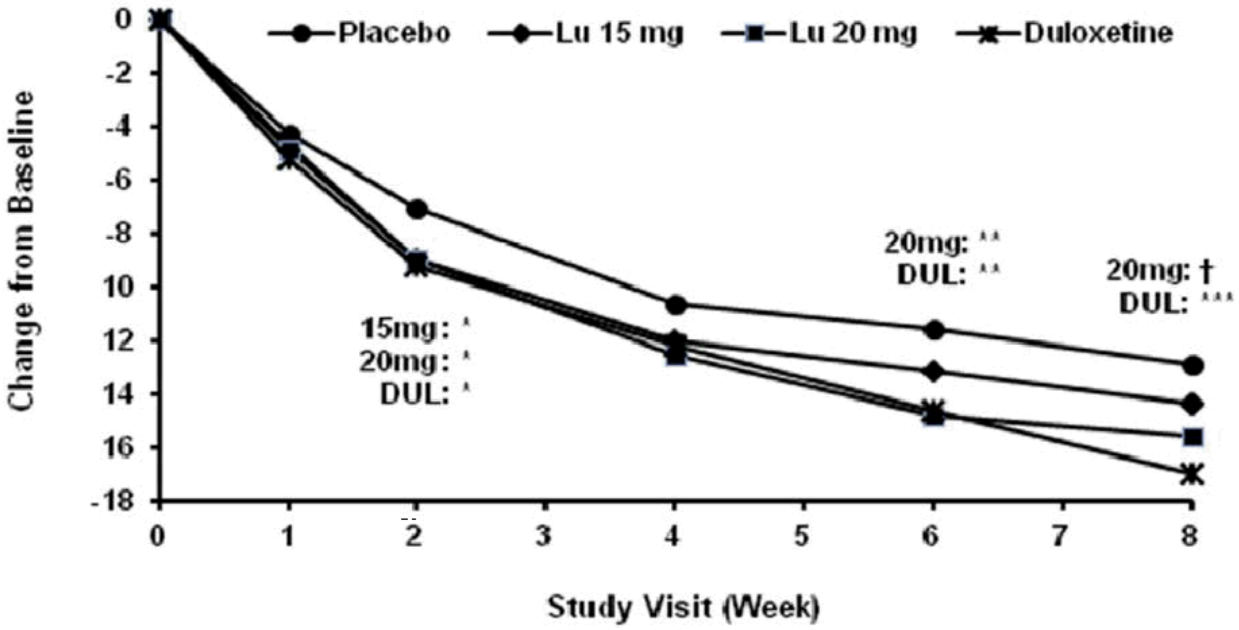
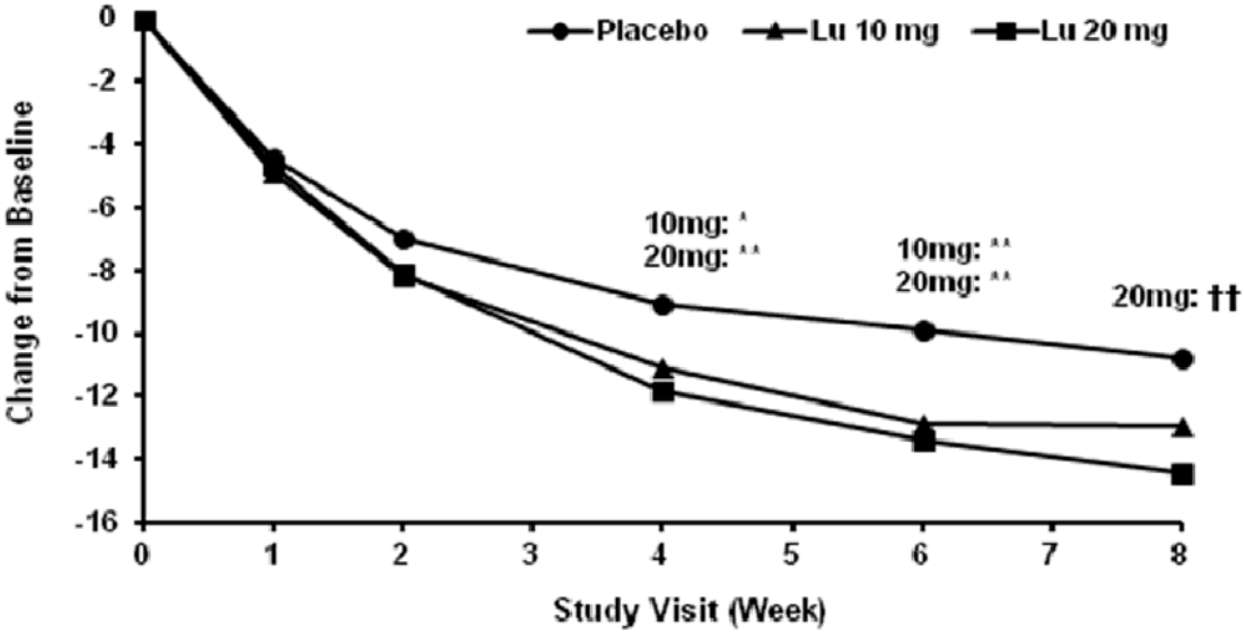
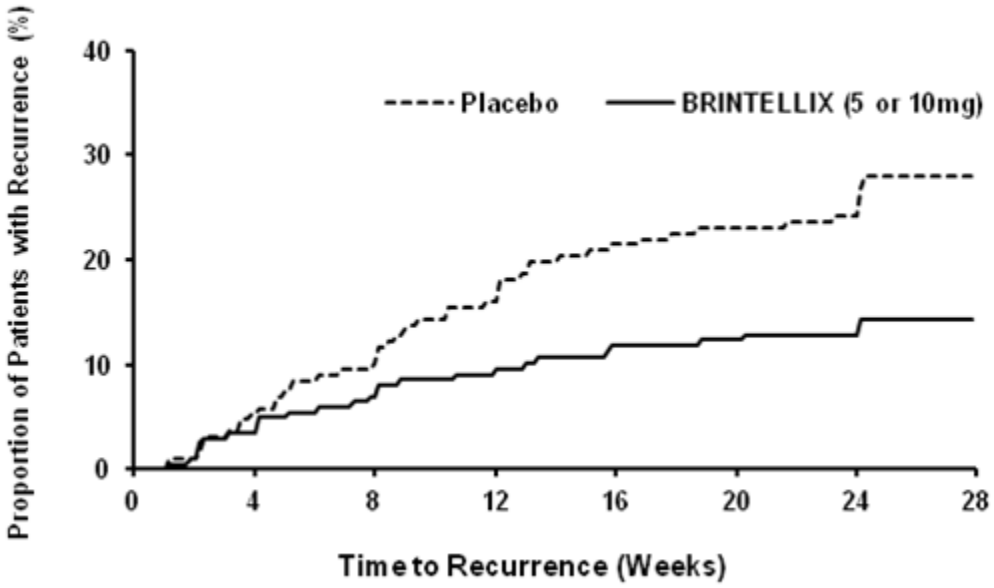


Figure 4: Change From Baseline in MADRS by Week (FAS, OC, MMRM) - Study 316 (US)



The maintenance (relapse prevention) study 11985A was carried out wholly OUS in patients in remission after a 12 week open-label treatment with 5 or 10 mg. Patients (n = 218) were then randomized to continuing their dose or to placebo. Time to relapse was significantly delayed (p = 0.003) by vortioxetine, as seen in the figure below from the approved labeling.

Figure 6. Kaplan-Meier Estimates of Proportion of Patients with Recurrence (Study 11985A)



There was little difference between patients on 5 or 10 mg. The possibility that higher doses are needed acutely in light of the long half-life of vortioxetine has led to a post-approval commitment by Takeda to conduct a US trial comparing 5, 10, and 20 mg as maintenance.

Extensive subgroup analyses of pooled data revealed the above described regional differences in effect, but no substantial effect of age or gender. There was some tendency for the lower doses to give better effect in whites but this did not persist at higher doses. There was no consistent relationship of effect size to baseline MADRS, particularly at the 15-20 mg doses.

III. Safety

I have little to add to Dr. Mathis' Division Director Review. GI effects were numerically greatest, and these were dose related.

The total safety database was substantial (7666 patients exposed with 2743 patient years). Nausea was the most common reason for discontinuation (2.2% vortioxetine, 3.5% duloxetine, 0.3% placebo) but vomiting also lead to discontinuation. Nausea declined with time, falling to about 10% on doses of 10 or 20 mg by the end of the study. There were no drug-attributable deaths or serious adverse events, (as described in Dr. Sellers' detailed review). Vortioxetine does appear able to cause the serotonin syndrome (one possible case). There was no increase in suicidal ideation or behavior.

As is usual in depression studies, sexual dysfunction was reported infrequently, but the Arizona Sexual Experience scale (ASEX) was used in 7 of the placebo-controlled trials and revealed dose-related sexual dysfunction in males and females, as shown in Table 3 of labeling.

Table 3

Table 3. ASEX Incidence of Treatment Emergent Sexual Dysfunction*					
	BRINTELLIX 5 mg/day N=65:67†	**BRINTELLIX 10 mg/day** N=94:86†	**BRINTELLIX 15 mg/day** N=57:67†	**BRINTELLIX 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

IV. Conclusion

Vortioxetine is an effective anti-depressant for treatment of acute depression and for maintenance. It appears generally similar in overall effect to other agents but adequately powered comparison studies have not yet been conducted. There is hope that the maintenance dose of 5-10 mg that was effective in a trial outside the US will prove effective here in a maintenance study that Takeda has committed to conducting. The labeling for vortioxetine has several features not included in previous antidepressant labeling, notably 1) a substantial discussion of clinical trial results, showing both US and OUS data and some interesting differences between them, 2) a clear display of time to effect, illustrated by the US study considered most relevant, and 3) a much more detailed description of sexual dysfunction data based on ASEX data, giving far more sensitive information than unstructured adverse event data.

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/s/

ROBERT TEMPLE
09/30/2013