CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204447Orig1s000

SUMMARY REVIEW

M E M O R A N D U M DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: 11 September 2013

FROM: Mitchell V. Mathis, M.D.
Acting Director
Division of Psychiatry Products, HFD-130

TO: File NDA 204447 [28 Sep 2012 submission]

SUBJECT: Approval recommendation for vortioxetine hydrobromide (Brintellix) for the treatment of major depressive disorder

Background and Summary
Vortioxetine is a serotonergic drug with a mechanism of action that is not fully understood but is likely related to its enhancement of serotonergic activity in the brain via the blocking of serotonin reuptake (i.e., selective serotonin reuptake inhibitor action); it is also an antagonist at 5-HT3 receptors, but the role of this activity in treating depression, if any, is unknown.

The sponsor submitted ten short-term studies (five conducted exclusively in the US) and one relapse-prevention study in adults to support the indication of treatment of major depressive disorder (MDD). Six of the ten short-term studies were positive (for at least one dose of vortioxetine), as was the relapse prevention study. The clinical team spent a good deal of time discussing the effective dose range because studies conducted overseas demonstrated efficacy at lower doses than the dose that was effective in the US; the relapse prevention study was conducted overseas and was also positive at doses lower than those shown effective in US patients in the acute depression trials.

Safety findings were largely consistent with what we know about selective serotonin reuptake inhibitors (SSRIs); these have been labeled and are discussed in more detail below and in the clinical team memos.

Chemistry Manufacturing and Controls (CMC)
Drs. Wilson-Lee and Mahayni recommend approval of this NDA. Vortioxetine is a new chemical class of psychotropic: bis-aryl-sulfanyl amine. The tablets are immediate-release and are formulated as 5 mg, 10 mg, 15 mg, and 20 mg strengths. The drug product contains no novel excipients. The facilities inspections were completed by the Office of Compliance and they determined that the drug substance, drug product, and packaging facilities are adequate to support approval.

Nonclinical Pharmacology/Toxicology
Dr. Dow conducted the review and recommends approval. General toxicology studies were conducted in rat and dog to support chronic use of vortioxetine. Convulsions were noted in rats and

dogs at 195 and 16 times, respectively, the maximum recommended human dose (MRHD), but seizures were not seen in the chronic rat and dog studies at does 39 and 12 times, respectively, the MRHD. There was a potential genotoxic impurity noted early in the review cycle but this issue was resolved (maximum daily dose below the level of regulatory concern) during the review cycle.

Carcinogenesis was not observed in mice exposed for 2 years at doses up to 12 times (in males) and 24 times (in females) the MRHD. Vortioxetine was not genotoxic in the Ames test. Fertility was not impaired in rats at does up to 58 times the MRHD. Dr. Dow and her team have made several edits to labeling (including mechanism of action) which have been agreed to by the sponsor.

Office of Clinical Pharmacology (OCP)
Thirty-two studies were submitted for OCP review. Drs. Jackson (OCP) and Zhang (pharmacometrics) have both recommended that the product be approved.

Vortioxetine is extensively metabolized to pharmacologically inactive compounds by multiple cytochrome P450 enzymes, but it is primarily metabolized by CYP2D6 (poor CYP2D6 metabolizers have approximately twice the plasma concentrations of vortioxetine seen in comparably dosed extensive metabolizers). Labeling has been edited to adjust dosing for patients on inhibitors or inducers of 2D6. Mild and moderate hepatic impairment and renal impairment, including end-stage renal disease, did not change the pharmacokinetics of vortioxetine significantly enough to recommend lower doses. We have requested that the sponsor characterize the pharmacokinetics of vortioxetine in a population with severe hepatic impairment post-marketing.

No food effect was identified. Plasma protein binding is about 98%.

The pharmacological activity of vortioxetine appears to reside in the parent drug. The pharmacokinetics of vortioxetine (over the range of 2.5 mg – 60 mg per day) are linear and dose-proportional. The mean half-life of vortioxetine is 66 hours; accumulation results in a steady state concentration 5 times higher (than the concentration after dose initiation) after two weeks of taking the drug daily.

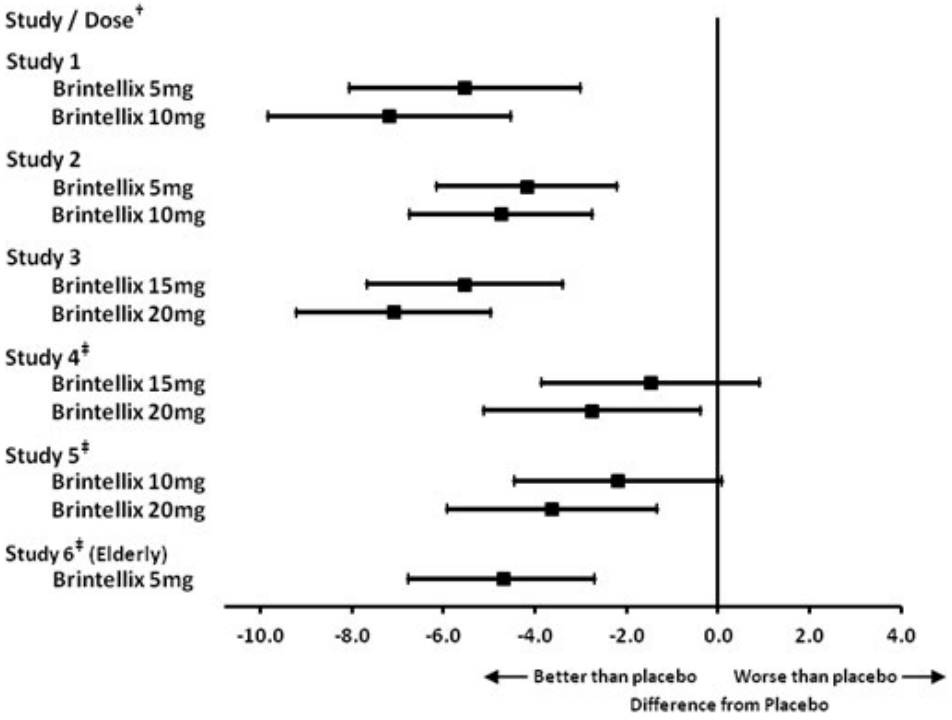
Clinical/Statistical
Drs. Sellers and Zhang (clinical) and Dr. Kordzakhia (statistics) evaluated the six positive short-term studies as well as the single positive maintenance study submitted to support this application. They have concluded that the drug has efficacy for treating MDD and that the safety profile has been characterized sufficiently to write an informative label and Medication Guide. They had some concern about which doses to recommend because of the difference in dose required to demonstrate efficacy in the US compared to the rest of the world (ROW). Twenty milligrams per day is the most consistently positive dose in Americans, whereas data from overseas support doses as low as 5 mg/day (see discussion below). In the end, it was determined that this was not an approval issue, but rather is a reason for careful labeling instructions to inform physicians that the 20 mg/day dose has demonstrated the most consistent efficacy in US patients, and therefore, that the target dose should be 20 mg in the absence of tolerability issues. The label is clear on this recommendation for dosing.

Efficacy—Acute Treatment
All of the short-term efficacy trials were multicenter, double-blind, randomized, placebo-controlled, parallel-group fixed dose studies of 6-8 weeks duration in adult patients with major depressive

disorder (MDD). Five of the six positive trials had an active comparator, and one study was done in elderly patients. The primary endpoint was either change from baseline to endpoint in HAMD24 or MADRS. Multiple secondary endpoints were explored by the sponsor. The positive maintenance study was the typical randomized withdrawal design and the primary endpoint was time to relapse (this was a non-US study at 5mg and 10 mg).

Summary of short-term vortioxetine study results (included in labeling):

Improvement* on MADRS Total Score vs. Placebo in 6 to 8 Week Studies



*Difference from Placebo in Mean Change from Baseline on MADRS Total Score at Week 6 or 8 (MMRM).
†Results are from mixed model for repeated measures analysis. In Studies 1 and 6 the primary analysis was not MMRM and in Studies 2 and 6 the primary efficacy measure was not based on MADRS
‡Study was conducted entirely in the US (4 and 5) or globally with US sites (6)

From the figure above, it is clear that each dose from 5 mg/day through 20 mg/day has demonstrated efficacy in at least one study. As part of the review, the team focused on the two US studies (Study 4 and Study 5 above) because these higher-dose studies were able to statistically demonstrate US efficacy only at the 20 mg/day dose, although a trend toward efficacy is evident at lower doses in these studies (Study 5, in fact, gave a positive result at 10 mg at 5 weeks). There were two US studies at 5 mg/day, neither showed an effect although an active control was effective in one of these studies. No differences in the populations being studied (US vs. ex-US) were identified, yet the replicated US results support a 20 mg/day dose. Labeling will reflect these regional differences and that the dose known to have efficacy in the US is 20 mg/day.

These same results are given in tabular format below (included in labeling):

Primary Efficacy Results of 6 Week to 8 Week Clinical Trials

Study No. [Primary Measure]	Treatment Group	Number of Patients	Mean Baseline Score (SD)	LS Mean Change from Baseline (SE)	Placebo-subtracted Difference† (95% CI)
Study 1 [MADRS] Non-US Study	BRINTELLIX (5 mg/day)‡	108	34.1 (2.6)	-20.4 (1.0)	-5.9 (-8.6, -3.2)
	BRINTELLIX (10 mg/day)‡	100	34.0 (2.8)	-20.2 (1.0)	-5.7 (-8.5, -2.9)
	Placebo	105	33.9 (2.7)	-14.5 (1.0)	--
Study 2 [HAMD-24] Non-US Study	BRINTELLIX (5 mg/day)	139	32.2 (5.0)	-15.4 (0.7)	-4.1 (-6.2, -2.1)
	BRINTELLIX (10 mg/day)‡	139	33.1 (4.8)	-16.2 (0.8)	-4.9 (-7.0, -2.9)
	Placebo	139	32.7 (4.4)	-11.3 (0.7)	--
Study 3 [MADRS] Non-US Study	BRINTELLIX (15 mg/day)‡	149	31.8 (3.4)	-17.2 (0.8)	-5.5 (-7.7, -3.4)
	BRINTELLIX (20 mg/day)‡	151	31.2 (3.4)	-18.8 (0.8)	-7.1 (-9.2, -5.0)
	Placebo	158	31.5 (3.6)	-11.7 (0.8)	--
Study 4 [MADRS] US Study	BRINTELLIX (15 mg/day)	145	31.9 (4.1)	-14.3 (0.9)	-1.5 (-3.9, 0.9)
	BRINTELLIX (20 mg/day)‡	147	32.0 (4.4)	-15.6 (0.9)	-2.8 (-5.1, -0.4)
	Placebo	153	31.5 (4.2)	-12.8 (0.8)	--
Study 5 [MADRS] US Study	BRINTELLIX (10 mg/day)	154	32.3 (4.5)	-13.0 (0.8)	-2.2 (-4.5, 0.1)
	BRINTELLIX (20 mg/day)‡	148	32.5 (4.3)	-14.4 (0.9)	-3.6 (-5.9, -1.4)
	Placebo	155	32.0 (4.0)	-10.8 (0.8)	--
Study 6 (elderly) [HAMD-24] US and Non-US	BRINTELLIX (5 mg/day)‡	155	29.2 (5.0)	-13.7 (0.7)	-3.3 (-5.3, -1.3)
	Placebo	145	29.4 (5.1)	-10.3 (0.8)	--

SD: standard deviation; SE: standard error; LS Mean: least-squares mean; CI: unadjusted confidence interval.
†Difference (drug minus placebo) in least-squares mean change from baseline.
‡ Doses that are statistically significantly superior to placebo after adjusting for multiplicity.

Results including active comparator and negative/failed studies:

Summary Results from 10 Short-Term MDD Trials

Study No./ Region	Main Inclusion Criteria	Results of Study Drug Doses (mg) vs. PBO	Overall Study Results
11492A/Europe, Australia, Canada, Asia	18-65 years MADRS≥30	BRINTELLIX 5 mg/day vs. PBO p<0.001 BRINTELLIX 10 mg/day vs. PBO p<0.001 Venlafaxine 225 mg/day vs. PBO p<0.001	Positive
305/Europe Asia, Australia, South Africa	18-75 years MADRS≥26	BRINTELLIX 5 mg/day vs. PBO p<0.001 BRINTELLIX 10 mg/day vs. PBO p<0.001	Positive
13267A/ Europe, South Africa	18-75 years MADRS≥26 and CGI-S≥4	BRINTELLIX 15 mg/day vs. PBO p<0.0001 BRINTELLIX 20 mg/day vs. PBO p<0.0001 Duloxetine 60mg/day vs. PBO p<0.0001	Positive
315/ US	18-75 years MADRS≥26 and CGI-S≥4	BRINTELLIX 15 mg/day vs. PBO NS (p=0.224) BRINTELLIX 20 mg/day vs. PBO p=0.023 Duloxetine 60mg/day vs. PBO p<0.001	Positive
316/ US	18-75 years MADRS≥26 and CGI-S≥4	BRINTELLIX 10 mg/day vs. PBO NS (p=0.058) BRINTELLIX 20 mg/day vs. PBO p=0.002	Positive
12541A Elderly / Europe, Canada, US	≥65 years MADRS≥26	BRINTELLIX 5 mg/day vs. PBO p=0.0011 Duloxetine 60 mg/day vs. PBO p<0.001	Positive
11984A/Europe, Canada, Asia, Australia	18-75 years MADRS≥26	BRINTELLIX 5 mg/day vs. PBO NS (p=0.132) BRINTELLIX 10 mg/day vs. PBO NS (p=0.185) Duloxetine 60mg/day vs. PBO NS (p=0.074)	Failed
317/US	18-75 years MADRS≥26	BRINTELLIX 10 mg/day vs. PBO NS (p=0.597) BRINTELLIX 15 mg/day vs. PBO NS (p=0.745)	Negative
303/ US	18-75 years MADRS≥30	BRINTELLIX 5 mg/day vs. PBO NS (p=0.407)	Negative
304/US	18-75 years MADRS≥22	BRINTELLIX 5 mg/day vs. PBO NS (p=0.577) Duloxetine 60 mg/day vs. PBO p=0.005	Negative

Efficacy by dose and region for positive efficacy studies:

Study Number	Primary Endpoint	Dose				
		1mg	5mg	10mg	15mg	20mg
11492A	MADRS	**Region**: non-US, multi-regional including Canada. **Study Conduct Dates:** 08/2006-08/2007				
LS mean difference (SE)			-5.9 (1.4)	-5.7 (1.4)		
p-value (unadjusted)			<0.001	<0.001		
Significance (MCP adjusted)			**Yes**	**Yes**		
305	HAMD-24	**Region**: outside North America. **Study Conduct Dates**: 08/2008-08/2009				
LS mean difference (SE)		-3.5 (1.0)	-4.1 (1.0)	-4.9 (1.0)		
p-value (unadjusted)		<0.001	<0.001	<0.001		
Significance (MCP adjusted)		**N/A**[#]	**No**[*]	**Yes**		
13267A	MADRS	**Region**: outside North America. **Study Conduct Dates**: 05/2010-09/2011				
LS mean difference (SE)					-5.5 (1.1)	-7.1 (1.1)
p-value (unadjusted)					<0.001	<0.001
Significance (MCP adjusted)					**Yes**	**Yes**
315	MADRS	**Region**:US. **Study Conduct Dates**: 06/2010-02/2012				
LS mean difference (SE)					-1.5 (1.21)	-2.8 (1.21)
p-value (unadjusted)					0.224	0.023
Significance (MCP adjusted)					**No**	**Yes**
316	MADRS	**Region**:US. **Study Conduct Dates:** 07/2010-01/2012				
LS mean difference (SE)				-2.2 (1.15)		-3.6 (1.16)
p-value (unadjusted)				0.058		0.002
Significance (MCP adjusted)				**No**		**Yes**
12541A (elderly)	HAMD-24	**Region**: multi-regional, including US and Canada. **Study Conduct Dates**: 01/2009-02/2010				
LS mean difference (SE)			-3.3			
p-value (unadjusted)			0.001			
Significance (MCP adjusted)			**Yes**			

Source: Statistical reviewer's summary based on sponsor's clinical study reports

[*] Since 10mg dose was not statistically significantly different from placebo in the first key secondary variable in the testing sequence (SDS), the formal testing was stopped according to the pre-specified hierarchical multiple testing procedure. None of the subsequent null hypotheses (including hypotheses associated with 5mg dose) in the pre-specified testing hierarchy are considered statistically significantly different from placebo.

[#] 1mg arm was not formally tested against placebo.

As can be seen from the tables above, there is a difference between the US and the rest of the world (ROW) studies regarding effective dose. The three negative studies were all conducted in the US

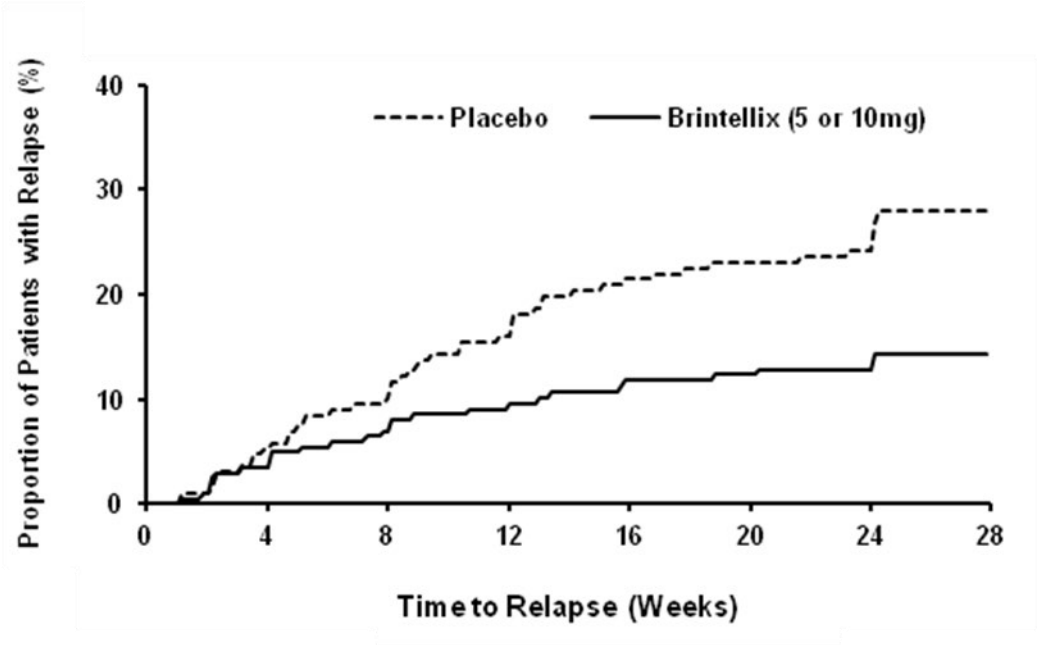
using vortioxetine doses of 5 mg, 10 mg, and 15 mg, and one of those trials (304) was able to differentiate duloxetine from placebo when vortioxetine 5 mg did not show a difference. US Studies 315 and 316 demonstrated a positive effect for vortioxetine 20 mg, but not 10 mg or 15 mg (although 10 mg in study 316 was nearly statistically significant). The clinical and statistical teams examined the data to try and identify why patients were responding to lower doses in the ROW compared to the US, but no definitive explanation was found. It is possible that US patients enrolling in clinical trials are somehow different than patients from the ROW, but exactly how they are different is unclear. What is clear is that we have replicated evidence that doses below 20 mg have not demonstrated efficacy in the US and that 20 mg should be the target dose in the US population, and the label reflects this.

Time to Onset of Effect

There has been a great deal of interest in examining when, in the course of early treatment, the effect of an antidepressant can be first identified. From the development program for vortioxetine, it is evident that statistically significant effects can be seen as early as 2 to 4 weeks after treatment initiation, and that the effect is generally maintained to endpoint. This information is valuable to patients and prescribers a typical time course from US Study 316 will be included in labeling.

Efficacy—Relapse Prevention

The longer-term efficacy of vortioxetine was demonstrated in a single relapse prevention study conducted outside of the US. Three hundred ninety six patients in remission (MADRS total score less than 10 at both weeks 10 and 12 of the stabilization period) were randomized 1:1 to continue drug (5 mg or 10 mg stabilization dose) or be blindly switched to placebo. The primary efficacy variable was time to relapse of depressive symptoms and the results are presented graphically below. Most vortioxetine patients were on 10 mg/day, but results for patients at both doses were similar.



Efficacy—Conclusions

The sponsor has presented sufficient evidence to demonstrate that vortioxetine is effective in treating and preventing relapse/recurrence in patients with MDD. The 20 mg dose is the only dose in US studies with adequate evidence of efficacy to recommend to US prescribers. The relapse prevention trial was not conducted in the US but was conducted in patients on a stable 5 mg or 10 mg dose of vortioxetine. We have no evidence that US patients, who as a group required 20 mg/day for acute treatment, would do well on a lower dose during the maintenance phase of treatment. The label will make this clear (the dose that worked acutely should be continued beyond the initial treatment period) and we will ask the sponsor to conduct a US randomized withdrawal trial, randomizing stable patients to different lower doses (or placebo) during the maintenance phase.

Safety

Exposure: There were 7666 subjects development (2743 patient-years) exposed to vortioxetine during this development program. Doses ranged from 1 mg/day to 75 mg/day in the phase 1 studies and up to 20 mg/day in phases 2 and 3. More than two thousand patients received vortioxetine for more than six months, and more than one thousand for at least a year.

Summary of Safety: Overall the safety profile was similar that of the SSRIs. Gastrointestinal symptoms are prominent with vortioxetine, with nausea, constipation, and vomiting seen at least twice as often on vortioxetine as on placebo. Nausea was the most commonly reported adverse reaction and was reported in 26-32% of drug patients vs. 9% of placebo patients. Nausea persistent to the end of the study was less common (about 10%) but did occur more often than on placebo.

Deaths: There were 6 deaths during the development program, none of which was considered related to drug by the clinical investigators or the review team.

Serious Adverse Events: From the short-term MDD trials, the overall incidence of serious adverse events was 1% for vortioxetine, 1.1% for duloxetine, and 0.9% for placebo. There were two convulsions reported in the vortioxetine group (both patients with prior traumatic brain injuries).

Adverse Events Leading to Discontinuation: The most common adverse event leading to discontinuation in the vortioxetine group was nausea: vortioxetine 2.2%, duloxetine 3.5%, placebo 0.3%. Other adverse events that led to discontinuation in the vortioxetine group were vomiting and suicidal ideation. Dr. Sellers has made the point that the nausea identified in the vortioxetine groups is longer-lasting than that seen with duloxetine, the active comparator, with approximately 10% of patients dosed with vortioxetine above 10 mg/day experiencing nausea that persisted to the end of the short-term trials.

Common and Dose-Related Adverse Reactions: Defined as occurring in at least 5% of patients and at a rate at least twice placebo, nausea, constipation, and vomiting were common and related to dose (see below).

Common Adverse Reactions: Defined as occurring in at least 2% of patients and in at least 2% more patients on drug than placebo were mainly gastrointestinal in nature (see below).

Common Adverse Reactions Occurring in ≥2% of Patients Treated with any Vortioxetine Dose and at Least 2% Greater than the Incidence in Placebo-treated Patients					
System Organ Class Preferred Term	**BRINTELLIX 5 mg/day**	**BRINTELLIX 10 mg/day**	**BRINTELLIX 15 mg/day**	**BRINTELLIX 20 mg/day**	**Placebo**
	N=1013 %	N=699 %	N=449 %	N=455 %	N=1621 %
Gastrointestinal disorders					
Nausea	21	26	32	32	9
Diarrhea	7	7	10	7	6
Dry mouth	7	7	6	8	6
Constipation	3	5	6	6	3
Vomiting	3	5	6	6	1
Flatulence	1	3	2	1	1
Nervous system disorders					
Dizziness	6	6	8	9	6
Psychiatric disorders					
Abnormal dreams	<1	<1	2	3	1
Skin and subcutaneous tissue disorders					
Pruritus*	1	2	3	3	1

*includes pruritus generalized

Abrupt Discontinuation Symptoms: The sponsor assessed abrupt discontinuation symptoms with the DESS scale several of their placebo controlled studies. Adverse events (in at least 5% of patients on 15mg and occurring at at least twice the rate with placebo discontinuation) were: headache, muscle tension/stiffness, mood swings, sudden anger outburst, dizziness and rhinorrhea. The label will instruct physicians to incrementally drop the dose to 10 mg prior to discontinuation when possible to avoid the discontinuation reactions.

Labeling

Labeling was extensively modified by the review teams and included input from the Office of Prescription Drug Promotion (OPDP), Pediatric and Maternal Health Staff (PMHS), and the Patient Labeling Team. All recommendations have been incorporated into the final negotiated label and Medication Guide. Labeling is in PLR format and has been negotiated to division standards.

Inspections

Six clinical study sites were inspected and no significant deficiencies were found. The Office of Scientific Investigation deemed the data presented for review to be reliable.

Postmarketing Requirements/Commitments

We have negotiated and the sponsor has agreed to conduct the following studies post-marketing:

1. An in vivo study in healthy subjects with severe hepatic impairment to evaluate the effect of reduced hepatic function on the PK of a 5 mg dose of vortioxetine.
2. An in vitro determination of parent and major metabolite inhibition of major transporters.
3. Pediatric studies as a PREA requirement (sponsor has already submitted a pediatric plan).

4. A relapse prevention study in US patients randomizing stable patients to different doses of vortioxetine (or placebo) during the double-blind maintenance phase of the typical randomized withdrawal trial to determine maintenance efficacy.

Conclusions and Recommendations

Sufficient information has been submitted to conclude that vortioxetine is safe and effective to treat major depressive disorder. The dose with evidence of efficacy in US patients is 20 mg/day and labeling will inform physicians of this. There are several gastrointestinal adverse reactions that prevent starting patients at 20 mg, but patients should be moved from lower doses to 20 mg/day depending on tolerance. Whether a dose lower than 20 mg/day is sufficient to prevent relapse will be assessed post-marketing. There are multiple safety concerns and warnings, but these have been prominently and adequately labeled as with other drugs in the class.

The labeling and Medication Guide have been negotiated to current Division standards.

The sponsor has agreed to labeling and the post-marketing commitments and requirements; this application should be approved by the PDUFA date.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MITCHELL V Mathis
09/16/2013