CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022567Orig1s000

OTHER REVIEW(S)

Medical Officer's Consultative Review of NDA 22-567
Ophthalmology Consult

NDA 22-567		**Submission date:**	7/7/10
Ophthalmology Consult		**Review date:**	1/7/11

Sponsor: PGxHealth, LLC

Drug: Vilazodone

Pharmacologic Category: Serotonin reuptake inhibitor

Proposed Indication: Major depressive disorders

Requested:

The sponsor has submitted an original NDA (22567) for vilazodone in the treatment of depression. Vilazodone has two serotonergic mechanisms of action: it is an SSRI as well as an agonist at the 5-HT1A receptor. We would appreciate your assessment of the ophthalmologic findings and conclusions submitted by the sponsor.

Background:

The sponsor has provided data from five 8-week clinical studies and one 52-week open-label study of vilazodone. In addition, the sponsor has provided an independent expert's review of the ophthalmologic data. In the sponsor's opinion, the results of the ophthalmologic assessments did not demonstrate clinically significant changes in 'eye health' or ocular function in subjects treated with vilazodone. The report indicates that the presence of treatment-emergent cataracts was identified by slit-lamp biomicroscopy in 22 subject-eyes among 12 subjects. For cortical, nuclear sclerotic, and posterior subcapsular cataract types, the number of subject-eyes that shifted from negative at baseline to positive at the end of treatment was 'small'. Of 110 subjects with cataract at baseline, the overall cataract severity was determined to have worsened for 14 (12.7%) subjects and to have remained stable (change in summed score <0) for 96 (87.3%) subjects at end of treatment.

In a zip file, we have included: two previous ophthalmology consults, two safety summaries containing relevant ophthalmologic data, and the study report for the 52-week clinical study.

We have the following questions:
1) What is your assessment of the ophthalmologic findings?
2) Has the sponsor adequately assessed the ophthalmologic safety profile of vilazodone?
3) Could the ophthalmologic risks be managed through labeling? Would you recommend any specific labeling?
4) Would you recommend that we request any additional information from the sponsor?

The Clinical reviewer is Cheri Lindberg, M.D., and the TL is Robert Levin, M.D.; the Pharmacology/Toxicology (non-clinical) reviewer is Violetta Klimek, Ph.D., and the TL is Linda Fossom, Ph.D. Let me know if you have any questions to send to the sponsor. The link to the NDA original application can be found at: \\CDSESUB1\EVSPROD\NDA022567\022567.ENX
We will also send a zip file that contains relevant summaries and data.

Reviewer's Comments: *Responses in this consult will be limited to areas of ophthalmologic concern.*

Phase 2 Studies:

Table 5: Ocular Drying Effects

Treatment	Days on Medication	Eyes per category	Schirmer Value < 10 mm			Schirmer Value < 5 mm		
			# eyes	%	% change from previous visit	# eyes	%	% change from previous visit
Placebo	Baseline	n=1130	278	24.60%		92	8.14%	
	Visit 2	n=972	232	23.87%	-0.73%	82	8.44%	0.29%
	Visit 3	n=812	192	23.65%	-0.96%	66	8.13%	-0.01%
Citalopram	Baseline	n=248	48	19.35%		15	6.05%	
	Visit 2	n=202	35	17.33%	-2.03%	9	4.46%	-1.59%
	Visit 3	n=160	48	30.00%	10.65%	10	6.25%	0.20%
Fluoxetine	Baseline	n=358	112	31.28%		49	13.69%	
	Visit 2	n=276	97	35.14%	3.86%	42	15.22%	1.53%
	Visit 3	n=276	86	31.16%	-0.13%	37	13.41%	-0.28%
Vilazodone 5 mg	Baseline	n=288	50	17.36%		18	6.25%	
	Visit 2	n=236	68	28.81%	11.45%	26	11.02%	4.77%
	Visit 3	n=254	81	31.89%	14.53%	22	8.66%	2.41%
Vilazodone 10 mg	Baseline	n=522	128	24.52%		44	8.43%	
	Visit 2	n=432	112	25.93%	1.40%	49	11.34%	2.91%
	Visit 3	n=424	131	30.90%	6.38%	55	12.97%	4.54%
Vilazodone 20 mg	Baseline	n=928	238	25.65%		78	8.41%	
	Visit 2	n=777	206	26.51%	0.87%	71	9.14%	0.73%
	Visit 3	n=716	194	27.09%	1.45%	62	8.66%	0.25%
Vilazodone 40-60 mg	Baseline	n=188	44	23.40%		13	6.91%	
	Visit 2	n=128	30	23.44%	0.03%	5	3.91%	-3.01%
	Visit 3	n=130	42	32.31%	8.90%	9	6.92%	0.01%
Vilazodone 80-100 mg	Baseline	n=224	83	37.05%		27	12.05%	
	Visit 2	n=122	48	39.34%	2.29%	18	14.75%	2.70%
	Visit 3	n=112	31	27.68%	-9.38%	10	8.93%	-3.13%

Table 5: Schirmer results are broken down per treatment arm to track any progressive effect of the test articles on lacrimation. The columnar values '# eyes' represents the number of eyes which had Schirmer scores of less than 10 mm. The percent is the incidence under 10 mm per treatment arm pre visit, and the '%change from previous visit' represents the increase in incidence of Schirmer values under 10 mm at that visit. Cells highlighted in red represent notable increases in incidence of dry eye at that visit.

Reviewer's Comments: *Multiple dose levels demonstrate decreasing tear product following use of vilazodone. Tear film deficiencies may account for some of the decreased vision and some of the corneal abnormalities.*

The following funduscopy findings were reported:

Retinal hemorrhage – 3 reports
Floaters -1 report
Abnormal cup – 2 reports
Vitreous detachment – 1
Microaneurysm – 1

Reviewer's Comments: *The relatively few reports and the nature of the reports do not suggest any retinal or vitreous problem related to the drug product.*

Study CLDA-07-DP-04

A One Year Open-Label Study Assessing the Safety and Tolerability of Vilazodone in Patients with Major Depressive Disorder

Ophthalmologic examinations were performed at baseline (Visit 1) and subsequently at Visits 11 (Week 24) and 18 (Week 52). Exams were performed at the early termination visits for patients withdrawing from the study. Evaluations included assessment of best corrected visual acuity as measured by manifest refraction and Snellen scoring, as well as slit-lamp biomicroscopy of the conjunctiva, iris, cornea, and lens. Dilated fundoscopy examinations of the macula, disc, and retinal vessels were performed and the presence/absence of pigments/naevi, exudates, microaneurysms, and/or hemorrhages were noted. Intraocular pressure was also measured at baseline and Week 52 (or at Early Termination [ET]).

Treatment emergent Adverse Events pertaining to the eye occurred in 97 patients (16.2%), the most common of which included dry eye (4.7%), vision blurred (4.0%), and lacrimation increased (1.2%).

Reviewer's Comments: *Dry eye can be contribute to both blurred vision and increased lacrimation.*

			Vilazodone Treatment Result			
			Right Eye		Left Eye	
Corneal Findings	N	Baseline	Normal	Abnormal	Normal	Abnormal
Visit 11/Week 24	310	Normal	288	5	288	5
		Abnormal	2	15	3	14
Visit 18/Week 52	247	Normal	231	4	227	8
		Abnormal	2	10	3	9

Reviewer's Comments: *These corneal findings are likely to be a result of the dry eye abnormalities.*

Lens/Cataract			Absent	Present	Absent	Present
Visit 11/Week 24	310	Absent	222	5	227	4
		Present	10	73	9	70
Visit 18/Week 52	247	Absent	171	6	175	6
		Present	8	62	7	59

Change from Baseline to End of Treatment in Overall Cataract Severity
All Patients with Cataracts at Baseline

Eye	N	Stable	Worsened
Right	110	100 (90.9%)	10 (9.1%)
Left	110	99 (90.0%)	11 (10.0%)
More Severe	110	96 (87.3%)	14 (12.7%)

Reviewer's Comments: *A 9-10% rate of cataract progression in one year is considered high. It is not possible to distinguish without a control group whether this is due a higher than normal rate in this population or due to the drug product.*

	N	Stable	2 Level Decrease	>2 Level Decrease
Right Eye				
Visit 11/Week 24	270	268	0	2
Visit 18/Week 52	213	212	1	0
Visit 18/Early Termination	118	117	0	1
End of Treatment	385	382	1	2
Left Eye				
Visit 11/Week 24	269	264	3	2
Visit 18/Week 52	214	210	4	0
Visit 18/Early Termination	115	112	2	1
End of Treatment	383	375	6	2

Other Ocular Adverse Events:
Among rare TEAEs, 1 subject (0.2%) reported an abnormal sensation in eye, considered mild in severity. Mild blepharitis was reported by 1 subject (0.2%). Mild eye irritation was reported by 2 subjects (0.3%). Increased lacrimation, rated as mild or moderate in severity, occurred in 7 subjects (1.2%). One subject temporarily discontinued study drug due to increased lacrimation. Photophobia was reported by 4 subjects (0.7%), and was considered to be mild or moderate in severity. No subject discontinued due to photophobia. Mild punctate keratitis was reported in 1 subject (0.2%). Reduced visual acuity, mild in intensity, was reported in 4 subjects (0.7%). Other reported events included moderate blepharospasm (1, 0.2%), mild-to-moderate transient blindness/temporary loss of vision (2, 0.3%), mild to moderate eye pain (4, 0.7%), mild eye swelling (2, 0.3%), mild eyelid disorder (2, 0.3%), mild eyelid margin crusting (2, 0.3%), mild myodesopsia (1, 0.2%), “mild” oculogyric crisis (1, 0.2%), mild eye pruritus (3, 0.5%), accommodation disorder (1, 0.2%), arteriosclerotic retinopathy (1, 0.2%), cataract (3, 0.5%), cortical cataract (1, 0.2%), conjunctival hemorrhage (3, 0.5%), conjunctivitis (4, 0.7%), allergic conjunctivitis (2, 0.3%), corneal infiltrates (1, 0.2%), corneal neovascularization (1, 0.2%), acquired dacryostenosis (1, 0.2), eye discharge (2, 0.3%), eye hemorrhage (1, 0.2%), giant papillary conjunctivitis (1, 0.2%), lacrimal disorder (1, 0.2%), ocular hyperaemia (2, 0.3%), ocular hypertension (1, 0.2%), retinal hemorrhage (1, 0.2%), and retinal tear (1, 0.2%)and mild-to-moderate visual impairment (4, 0.7%). One subject temporarily discontinued, and another subject permanently discontinued due to moderate visual impairment.

Reviewer's Comments: *There is no particular pattern to these events and the frequency is consistent with events typically seen in a population of this age range (Mean Age was 43 ±13, Range 18-70, Median 44).*

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