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Testimony Before the FDA's Advisory Committee on Reproductive Health Drugs on New Drug Application (NDA) 204-516, Paroxetine Mesylate Capsules for Treatment of Vasomotor Symptoms Associated With Menopause

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March 4, 2013

I am Dr. Michael Carome, Deputy Director of Public Citizen's Health Research Group (HRG), testifying on behalf of myself; Dr. Sammy Almashat, HRG Researcher; and Dr. Sidney Wolfe, the HRG Director. We have no financial conflicts of interest.

We strongly oppose the Food and Drug Administration's (FDA's) approval of paroxetine for treatment of moderate to severe vasomotor symptoms (VMS, which includes hot flashes and flushing) due to menopause — a very bothersome condition, but a non-life-threatening and self-limited one — because:

(1) With respect to benefits, the phase 3 clinical trials failed to demonstrate any evidence of clinically significant benefits for paroxetine in comparison to placebo;

(2) With respect to risks, paroxetine, a psychotropic drug, has many well-documented risks that far outweigh the trivial benefits of the drug for the proposed indication.

Efficacy Deficiencies

As seen in Table 7 of the FDA background document (copy attached), in the two phase 3 trials, the reduction in the daily frequency of moderate to severe VMS at week 12 from baseline with paroxetine versus placebo, although statistically significant, was not clinically significant (-0.9 and -1.7, with a mean baseline daily frequency of 10).[1] The one study that evaluated whether the reduction in frequency was clinically meaningful failed to show clinically meaningful changes at week 12. The reduction in VMS severity at week 12 was not statistically significant in one trial and was trivial (-0.05) in the other trial.

[1] The Food and Drug Administration. Background document for meeting of Advisory Committee for Reproductive Health Drugs, March 4, 2013, NDA 204-516, paroxetine mesylate capsules 7.5 mg. Page 24. http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/ReproductiveHealthDrugsAdvisoryCommittee/UCM341590.pdf. Accessed March 1, 2013.

Safety Problems

(1) The current FDA-approved label for paroxetine lists multiple adverse reactions, some potentially life-threatening, including:[2]

- Serotonin syndrome, which can lead to coma or death
- Seizures or convulsions
- Manic episodes
- Hyponatremia (low blood sodium level)
- Bleeding
- Potential reduction in efficacy of tamoxifen (which is important because women with breast cancer or a high risk of breast cancer, who may be taking tamoxifen, constitute a significant target population for non-hormonal VMS therapies)

(2) The label also lists common adverse events that led to discontinuation of paroxetine in clinical trials for other now-approved indications with a two-fold or greater frequency than placebo, which include:[3]

- Somnolence
- Insomnia
- Agitation
- Tremor
- Dizziness
- Constipation
- Sexual problems, including decreased libido in many trials

(3) Safety data from the phase 3 trials for this NDA revealed that suicidal ideation, suicidal attempt, depressed mood, or elevated mood led to drug discontinuation in five paroxetine subjects and no placebo subjects.[4] The FDA noted that these were plausibly related to the study drug. It should be noted that the trial protocol excluded subjects with a history of suicidal behavior or ideation, as well as other psychiatric diagnoses, and these adverse events occurred within just 24 weeks of beginning paroxetine therapy.

[2] Noven Therapeutics, LLC. FDA-approved drug label for PEXEVA. Revised December 2012. Available in FDA background document for meeting of Advisory Committee for Reproductive Health Drugs, March 4, 2013, NDA 204-516, paroxetine mesylate capsules 7.5 mg. Pages 45-70. http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/ReproductiveHealthDrugsAdvisoryCommittee/UCM341590.pdf. Accessed March 1, 2013.

[3] *Ibid*.

[4] The Food and Drug Administration. Background document for meeting of Advisory Committee for Reproductive Health Drugs, March 4, 2013, NDA 204-516, paroxetine mesylate capsules 7.5 mg. Page 33. http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/ReproductiveHealthDrugsAdvisoryCommittee/UCM341590.pdf. Accessed March 1, 2013.

(4) A recently published review from the Nordic Cochrane Center found that withdrawal reactions to selective serotonin re-uptake inhibitors were very similar to those for benzodiazepines.[5] The paroxetine Medication Guide also warns that:[6]

> Stopping PEXEVA too quickly may cause serious symptoms including
> - anxiety, irritability, high or low mood, feeling restless, or changes in sleep habits
> - headache, sweating, nausea, dizziness
> - electric shock-like sensations, shaking, confusion

In conclusion:

(1) Based on the sponsor's and FDA's analyses, paroxetine is at best marginally effective in treating moderate to severe VMS due to menopause, as the change from baseline in VMS frequency or severity seen with paroxetine versus placebo is not clinically meaningful.

(2) Given the absence of evidence demonstrating clinically significant benefits and the known risks of the drug, the high risk-to-benefit ratio for paroxetine is clearly unacceptable to support approval of this product for the proposed indication.

[5] Nielsen M, Hansen EH, Gotzsche PC. What is the difference between dependence and withdrawal reactions? A comparison of benzodiazepines and selective serotonin re-uptake inhibitors. Addiction. 2012;107(5):900-908.
[6] Noven Therapeutics, LLC. FDA-approved drug label for PEXEVA. Revised December 2012. Available in FDA background document for meeting of Advisory Committee for Reproductive Health Drugs, March 4, 2013, NDA 204-516, paroxetine mesylate capsules 7.5 mg. Pages 45-70. http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/ReproductiveHealthDrugsAdvisoryCommittee/UCM341590.pdf. Accessed March 1, 2013.

Table 7 Changes in Daily Frequency and Severity of Moderate to Severe Hot Flushes at Weeks 4 and 12 (MITT Population)

Study	Frequency			Severity		
	Paroxetine mesylate	Placebo	Treatment Difference	Paroxetine mesylate	Placebo	Treatment Difference
Study N30-003						
Baseline						
N	301	305		301	305	
Median	10.4	10.4		2.54	2.54	
Change from baseline						
Week 4						
Median	-4.3	-3.1	-1.2	-0.05	0.00	-0.05
p-value#			<0.0001			0.002
Week 12						
Median	-5.9	-5.0	-0.9	-0.06	-0.02	-0.04
p-value#			0.009			0.166
Study N30-004						
Baseline						
N	284	284		284	284	
Median	9.9	9.6		2.53	2.53	
Change from baseline						
Week 4						
Median	-3.8	-2.5	-1.3	-0.04	-0.01	-0.03
p-value#			<0.0001			0.037
Week 12						
Median	-5.6	-3.9	-1.7	-0.05	0.00	-0.05
p-value#			0.0001			0.006

* **Treatment Difference is the observed difference between medians.**
 # p-value is obtained from rank-ANCOVA model.
Sources: Applicant's Table 14.2.2.01A1 and Table 14.2.2.01_SEVA1 in n30-003-responsetables.pdf (dated 12/07/2012); Table 14.2.2.01A1 and Table 14.2.2.01_SEVA1 in n30-003-responsetables.pdf (dated 12/07/2012); FDA Reviewer's analysis