Presentation of Sarah Sorscher, Public Citizen's Health Research Group, Before the Food and Drug Administration Psychopharmacologic Drugs Advisory Committee

December 1, 2015

[Slide 1]

Good afternoon, my name is Sarah Sorscher and I am a researcher with Public Citizen's Health Research Group. I have no financial conflicts of interest.

I am here today because Public Citizen is concerned that approval of gepirone would represent an unprecedented step backwards, effectively weakening the FDA's standards for approval of these drugs, and possibly others.

[Slide 2]

The gepirone development program is notable not only for the sheer number of failed and negative trials, but also for the direction of treatment effect trends. This table includes the nine completed efficacy trials that were considered by the FDA in its efficacy review for gepirone, excluding the three trials that were terminated early.[1]

Of these nine completed efficacy trials, four showed trends in the wrong direction, with greater observed improvement in the placebo group compared with the group receiving gepirone. These appear in red on this slide. And while two trials did achieve positive results (displayed in blue), the possibility remains that these positive findings could be due to random chance.

[1] FDA Briefing Document, Psychopharmacologic Drugs Advisory Committee (PDAC) meeting, December 1, 2015. Pages 19-20. http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/PsychopharmacologicDrugsAdvisoryCommittee/UCM474540.pdf. Accessed November 30, 2015.

Gepirone: Phase 2/3 randomized placebo-controlled short-term efficacy trials for MDD (n=9)*				
	Trial No*	Protocol-specified outcome measure	Treatment Effect (Gep - Pbo difference)	p-value
1	ORG 134004	HAMD-25	0.87	0.42
2	ORG 134017	MADRS	0.5	0.65
3	ORG 134023	HAMD-17	0.13	0.9
4	ORG 134006	HAMD-25	0.06	0.95
5	ORG 134002	HAMD-17	-0.71	0.42
6	FK-GBE-008	HAMD-17	-1.38	0.2
7	CN105-053	HAMD-17	-2.00	0.19
8	FK-GBE-007	HAMD-17	-2.45	0.018
9	ORG 134001	HAMD-17	-2.47	0.013

* Three trials, 052, 078, and 083, are not included because they were terminated early.

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Gepirone's sponsor has cited four other drugs approved despite large numbers of failed or negative trials, suggesting the FDA is being unfair by denying approval in this case.[2, 3]

[2] Fabre-Kramer Pharmaceuticals. Gepirone hydrochloride extended-release tablets, NDA #21-164. Psychopharmacologic Drugs Advisory Committee Meeting Briefing Materials, December 1, 2015. Page 9. http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/PsychopharmacologicDrugsAdvisoryCommittee/UCM474542.pdf. Accessed November 30, 2015.

- Citalopram (CELEXA), approved in 1998
- Duloxetine (CYMBALTA), approved in 2004
- Desvenlafaxine (PRISTIQ), approved in 2008
- Vilazodone (VIIBRYD), approved in 2011

Yet the negative evidence in the gepirone development program is unprecedented even in relation to these drugs.

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This table is derived from data published by the FDA as part of the action package for approval of Citalopram (CELEXA).[4] It includes all of the Phase 2/3 randomized placebo-controlled short-term efficacy trials for depression considered by the FDA in its efficacy review, regardless of whether they were considered negative or failed by FDA or the sponsor. (Additional short-term trials were not considered by the FDA in support of efficacy because they did not involve subjects with depression, lacked a placebo control, or were terminated early[5]).

Many of these trials failed to achieve statistically significant results. Yet looking at treatment effect, even the failed trials invariably involved positive trends towards effectiveness for CELEXA. Two short-term trials showed positive results (shown in blue), and two additional positive long-term relapse-prevention trials, not shown here, also helped support approval in this case.[6]

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[3] FDA Briefing Document, Psychopharmacologic Drugs Advisory Committee (PDAC) meeting, December 1, 2015. Page 279 (Fabre-Kramer Slide). http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/PsychopharmacologicDrugsAdvisoryCommittee/UCM474540.pdf. Accessed November 30, 2015.

[4] Food and Drug Administration. Medical Review, citalopram (CELEXA). NDA # 20822. Part 1 Pages 19, 28, Part 2 pages 23-25. http://www.accessdata.fda.gov/drugsatfda_docs/nda/98/020822a.cfm. Accessed November 30, 2015.

[5] Food and Drug Administration. Medical Review, citalopram (CELEXA). NDA # 20822. Part 1 Pages 19, 28, Part 2 pages 23-25. http://www.accessdata.fda.gov/drugsatfda_docs/nda/98/020822a.cfm. Accessed November 30, 2015.

[6] Food and Drug Administration. Medical Review, citalopram (CELEXA). NDA # 20822. Part 1 Page 25, Part 2 pages 19, 22. http://www.accessdata.fda.gov/drugsatfda_docs/nda/98/020822a.cfm. Accessed November 30, 2015.

Citalopram (CELEXA): Phase 2/3 randomized placebo-controlled short-term efficacy trials for MDD (n=5)*				
	Trial No	Measure	Treatment Effect (Cit - Pbo difference)	p-value
1	89306	MADRS	-0.09 to -1.99**	0.96 to 0.31**
2	89303	HAM-D	-0.59 to -2.75**	0.75 to 0.12**
3	91206	HAM-D	-0.63 to -2.91**	0.51 to < 0.01**
4	86141	HAM-D	-1.38	0.32
5	85A	HAM-D	-3.32	0.0344

* Two trials, 86A and 87A, were not included because they were terminated early.

** A range of values are presented for trials that included multiple dosing groups

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These two tables are derived from the FDA approval package for duloxetine (CYMBALTA)[7] and Desvenlafaxine (PRISTIQ),[8] and again contain all Phase 2/3 placebo-controlled short-term depression trials considered by the FDA in the efficacy review.

What is notable in these tables is that while both drugs had many trials that failed to achieve significant results, all of these trials displayed consistently positive trends. In addition, each approval included four positive short-term studies, rather than two.

Duloxetine (CYMBALTA): Phase 2/3 rand. pbo-controlled short-term efficacy trials for MDD (n=8)				
	Trial Number	Measure	Treatment Effect (Dul - Pbo difference)	p-value
1	HMAQb	HAMD-17	-0.04	0.96
2	HMAYb	HAMD-17	-0.85 to -1.55*	0.54 to 0.19*
3	HMATa	HAMD-17	-1.14 to -1.23*	0.222 to 0.058*
4	HMATb	HAMD-17	-1.51 to -3.11*	0.15 to 0.003*
5	HMAQa	HAMD-17	-1.66	0.15
6	HMAYa	HAMD-17	-2.17 to -3.21*	0.007 to < 0.001*
7	HMBHb	HAMD-17	-2.17	0.024
8	HMBHa	HAMD-17	-4.09	< 0.001

[7] Food and Drug Administration. Medical Review, duloxetine hydrochloride (CYMBALTA), NDA # 21427. http://www.accessdata.fda.gov/drugsatfda_docs/nda/2004/021427_s000_Cymbalta.cfm. Accessed November 30, 2015.

[8] Food and Drug Administration. Medical Review, desvenlafaxine succinate (PRISTIQ), NDA #21992. http://www.accessdata.fda.gov/drugsatfda_docs/nda/2008/021992s000TOC.cfm. Accessed November 30, 2015.

Desvenlafaxine (PRISTIQ): Phase 2/3 rand. pbo-controlled short-term efficacy trials for MDD (n=9)				
	Trial Number	Measure	Treatment Effect (Des - Pbo difference)	p-value
1	317	HAMD-17	-0.7	0.49
2	309	HAMD-17	-0.9	0.38
3	332	HAMD	-1.47 to -1.97*	0.065 to 0.018*
4	320	HAMD-17	-1.6	0.08
5	306	HAMD-17	-1.9 to -2.8*	0.076 to 0.002*
6	333	HAMD	-2.5 to -3.0*	0.002 to <0.001*
7	308	HAMD-17	-4.2 to -5.4*	0.008 to 0.002*
8	304	HAMD-17	not published	0.28
9	223	HAMD-17	not published	0.52 to 0.59*

***A range of values are presented for trials that included multiple dosing groups**

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In fact, vilazodone (VIIBRYD) is the only other antidepressant to show any negative trends during clinical testing, although only two trials in the VIIBRYD development program showed such trends compared with four in development program for gepirone. Public Citizen is troubled by this approval. Nevertheless, the two pivotal trials for VIIBRYD included large enough enrollments[9] to arrive at very low p-values, providing some re-assurance that the positive results in this case were a true effect and not a statistical fluke.

[9] Trial CLDA-07-DP-04 included 463 subjects, and GNSC-04-DP-02 included 410. Food and Drug Administration. Medical Review, vilazodone hydrochloride (VIIBRYD), NDA # 22567. Pages 44 and 61. By contrast, the positive trials of gepirone, FK-GBE-007 and ORG 134001, included 238 and 202 subjects, respectively. FDA Briefing Document, Psychopharmacologic Drugs Advisory Committee (PDAC) meeting, December 1, 2015. Page 19. http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/PsychopharmacologicDrugsAdvisoryCommittee/UCM474540.pdf. Accessed November 30, 2015.

	Vilazodone (VIIBRYD): Phase 2/3 randomized placebo-controlled short-term efficacy trials of in MDD (n=7)			
	Trial Number	Measure	Treatment Effect (Vil- Pbo difference)	p-value
1	244	HAMD	0.76 to 0.15*	0.49 to 0.89*
2	248	HAMD	0.5 to -1.2*	0.18 to 0.80*
3	246	HAMD	-0.5 to -0.8*	0.41 to 0.58*
4	245	HAMD	-0.9 to 1.6*	0.13 to 0.65*
5	247	HAMD	-1.0	0.27
6	CLDA-07-DP-04	MADRS	-2.5	0.009
7	GNSC-04-DP-02	MADRS	-3.2	0.001
*** A range of values are presented for trials that included multiple dosing groups**				

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In addition to the unprecedented negative short-term evidence, it is also highly unusual to see a failed relapse prevention trial like the failed trial submitted in the gepirone application (ORG28709).[10] In fact, out of 12 drugs cited in today's briefing materials as having completed such trials,[11,12] failure occurred for only 1

[10] FDA Briefing Document, Psychopharmacologic Drugs Advisory Committee (PDAC) meeting, December 1, 2015. Page 28. http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/PsychopharmacologicDrugsAdvisoryCommittee/UCM474540.pdf. Accessed November 30, 2015.
[11] FDA Briefing Document, Psychopharmacologic Drugs Advisory Committee (PDAC) meeting, December 1, 2015. Page 100.

drug, levomilnacipran (FETZIMA), approved in 2013. Notably, that application also included four adequate, well-controlled positive short-term efficacy studies, which allowed the FDA to conclude that the drug was effective despite the negative finding in the relapse prevention trial.[13]

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Finally, FDA statisticians have pointed out that among the four trials of gepirone that included an active-controlled arm, active controls performed consistently better than gepirone or placebo. These trends remain troubling even acknowledging that they did not reach statistical significance using the pre-planned analysis.

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As the FDA has stated, each of these multiple failures from the gepirone clinical program is exceptionally rare for an FDA-approved antidepressant.[14] They are especially notable for a drug from a class in which no drug has previously proven effective for depression treatment.[15] If gepirone were approved, it would represent a large step backwards, creating an example that will no doubt be used to pressure the agency to approve future new drugs in spite of lack of substantial evidence of effectiveness.

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http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/PsychopharmacologicDrugsAdvisoryCommittee/UCM474540.pdf. Accessed November 30, 2015.

[12] Fabre-Kramer Pharmaceuticals. Gepirone hydrochloride extended-release tablets, NDA #21-164. Psychopharmacologic Drugs Advisory Committee Meeting Briefing Materials, December 1, 2015. Page 33. http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/PsychopharmacologicDrugsAdvisoryCommittee/UCM474542.pdf. Accessed November 30, 2015.

[13] Food and Drug Administration. Medical Review, levomilnacipran (FETZIMA), NDA #204168. Page 25. http://www.accessdata.fda.gov/drugsatfda_docs/nda/2013/204168Orig1s000TOC.cfm. Accessed November 30, 2015.

[14] FDA Briefing Document, Psychopharmacologic Drugs Advisory Committee (PDAC) meeting, December 1, 2015. Page 191. http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/PsychopharmacologicDrugsAdvisoryCommittee/UCM474540.pdf. Accessed November 30, 2015.

[15] FDA Briefing Document, Psychopharmacologic Drugs Advisory Committee (PDAC) meeting, December 1, 2015. Page 80. http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/PsychopharmacologicDrugsAdvisoryCommittee/UCM474540.pdf. Accessed November 30, 2015.

Depression is a serious condition that requires effective treatment. Regardless of this drug’s safety, it should not be approved without additional robust evidence of effectiveness.

Public Citizen urges you to vote against approval of this drug.