

DECLARATION OF JOSEPH GLENMULLEN, M.D.

I, Joseph Glenmullen, M.D., do hereby declare and state:

1. My name is Joseph Glenmullen. I am a Medical Doctor. I am a graduate of and clinical instructor in psychiatry at Harvard Medical School. I earned my Bachelor of Arts, *magna cum laude*, from Brown University in 1972. I am Board Certified in Psychiatry. I have also been in private clinical practice since 1986, and served as a psychiatrist for staff, students, and faculty at the Harvard Law School Health Services for 20 years. A copy of my current CV is attached hereto as Exhibit A.

2. I have taught and supervised medical students, social work interns, psychology fellows, and psychiatry residents at Cambridge Hospital/Harvard Medical School since 1988 and I have given lectures to residents in advanced psychopharmacology on antidepressant withdrawal.

3. I am a member on the Board of Directors of the New England Division of the American Foundation for Suicide Prevention and a member of the American Association of Suicidology. I am the author of two books on the side effects of antidepressants: Prozac Backlash: Overcoming the Dangers of Prozac, Zoloft, Paxil and Other Antidepressants with Safe, Effective Alternatives and The Antidepressant Solution: A Step-by-Step Guide to Safely Overcoming Antidepressant Withdrawal, Dependence, and "Addiction." I have been an invited

speaker in a number of forums on the subject of my books and the material contained therein, including giving lectures at Harvard to both students and peers on these topics. Since its approval in 2004, I have prescribed Cymbalta to patients who were already taking the drug (i.e., I have continued prescriptions for Cymbalta), but I typically do not newly prescribe Cymbalta to my patients because of its short half-life and propensity to cause withdrawal reactions. I was aware of Cymbalta's short half-life and generally of its propensity to induce withdrawal because of the research I had done for my book The Antidepressant Solution, which relates to withdrawal from antidepressants, published in 2005. I receive frequent inquiries about antidepressant withdrawal from both patients and healthcare professionals who have read my books.

4. Antidepressant withdrawal is a term used to describe those symptoms a patient may experience when they stop taking an antidepressant. These symptoms are not caused by an underlying mental condition, but are a reaction of the body to no longer having the antidepressant in the patient's system. These withdrawal symptoms can be so severe that patients can be required to continue taking the antidepressant simply to treat the symptoms. Lilly and its consultants have euphemistically characterized this physical dependency on the drug as "Antidepressant Discontinuation Syndrome." Schatzberg et al., "Serotonin

Reuptake Inhibitor Discontinuation Syndrome: A Hypothetical Definition,” *J. Clin. Psychiatry* 1997;58 (suppl 7): 5-10 (attached hereto as Exhibit C).

5. The frequency of withdrawal symptoms directly correlates with the time it takes for an antidepressant to wash out of a patient’s body, known as a drug’s “half-life.” The shorter the half-life of an antidepressant, the more likely a patient will suffer from withdrawal symptoms. In my book, The Antidepressant Solution, I provide tables listing the comparative half-lives of the modern antidepressants and the correlation between half-life and the frequency of withdrawal reactions in studies. I have reproduced the tables and attached them to my Declaration as Exhibit B [Table 5.1 and 5.2]. Cymbalta is not included in Table 5.2 because the published study of Cymbalta withdrawal (Perahia et al., described below) had not yet been published.

6. Cymbalta (generically known as duloxetine) is a serotonin and norepinephrine reuptake inhibitor which was approved by the U.S. Food and Drug Administration (“FDA”) for major depressive disorder in 2004. It has subsequently been approved for other disorders including Generalized Anxiety Disorder (GAD) in 2007, fibromyalgia in 2008, and musculoskeletal pain in 2010.

7. As indicated in Exhibit B, Cymbalta has one of the shortest half-lives (compared to many other leading antidepressants) and, thus, it would be expected to frequently cause withdrawal symptoms upon discontinuation.

8. According to a study published in the *Journal of Affective Disorders*<sup>1</sup>, a pooled analysis of six of Lilly's clinical trials showed 44% of patients discontinuing Cymbalta experienced withdrawal symptoms and that a significant percentage of those symptoms were moderate or severe. *See* Perahia, et al., "Symptoms Following Abrupt Discontinuation of Duloxetine Treatment in Patients with Major Depressive Disorder," 89 *J. of Affective Disorders* 207-12 (2005) (attached hereto as Exhibit D). At the time of its publication, I was not a subscriber to the *Journal of Affective Disorders* (nor am I a subscriber now) and only became aware of the article in conjunction with this litigation.

9. Importantly, Lilly *did not* use systematic monitoring with a withdrawal symptom checklist in the studies underlying Perahia's analysis, whereas in earlier Lilly-sponsored studies comparing Prozac to Paxil, Zoloft and Effexor, Lilly systematically monitored withdrawal using a symptom checklist. (See paragraph 28 below.) The methods section of the Perahia article states: "DEAEs [Discontinuation Emergent Adverse Events] were elicited by *non-probing* inquiry" and, in the discussion section, it states: "The main limitation of this review is that DEAEs were assessed by means of spontaneous reports rather than a

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<sup>1</sup> The *Journal of Affective Disorders* is a medical journal published out of the Netherlands. According to a search of the SJR medical journal ranking database, in 2005 when the Perahia article was published, the *Journal of Affective Disorders* was not on the list of 87 journals ranked in the United States in psychiatry and mental health, in other words, it appears readership in the United States was too low to make it onto this list. SCImago (2007) SJR – SCImago Journal & Country Rank, Retrieved July 17, 2013 from <http://www.scimagojr.com>.

symptoms checklist. The latter might be expected to produce *higher incident rates.*” Based on Cymbalta’s half-life, one would expect the true risk of withdrawal to be more likely in the range between 66% and 78% as illustrated by Exhibit B, Table 5.2.

10. A drug’s propensity to cause withdrawal symptoms and, ultimately, physical dependency is an important factor to consider in deciding whether to prescribe a particular antidepressant to any patient. Ultimately, the risks of withdrawal symptoms associated with a particular antidepressant must be considered by any doctor who might prescribe an antidepressant, and any patient who might decide to take an antidepressant.

11. Treating physicians prescribe medicines such as Cymbalta relying on the truth of the drug’s label (i.e., the prescribing information contained in the package insert and published in the Physicians’ Desk Reference, “PDR”). Rarely do treating physicians perform their own clinical studies or have time to research what other studies have been performed on a particular medication. Although treating physicians have access to other sources of information, such as pharmaceutical representative detailing, recommendations by fellow physicians, and medical journal publications, treating physicians rely on the label as an ultimate authority of a drug’s safety and efficacy. In fact, if a medical journal article were to conflict with the information contained on the drug’s label,

physicians would consider the label more authoritative than the publication since the label is FDA approved.

12. The label for Cymbalta in 2004 stated in relevant part:

Discontinuation of Treatment with Cymbalta – Discontinuation symptoms have been systematically evaluated in patients taking Cymbalta. Following abrupt discontinuation in placebo-controlled clinical trials of up to 9-weeks duration, the following symptoms occurred at a rate greater than or equal to 2% and at a significantly higher rate in duloxetine-treated patients compared to those discontinuing from placebo: dizziness; nausea; headache; paresthesia; vomiting; irritability; and nightmare.

13. In 2005, Lilly added “MDD” before “placebo-controlled clinical trials” so the label read (changes are in bold):

Discontinuation of Treatment with Cymbalta – Discontinuation symptoms have been systematically evaluated in patients taking Cymbalta. Following abrupt discontinuation in **MDD** placebo-controlled clinical trials of up to 9-weeks duration, the following symptoms occurred at a rate greater than or equal to 2% and at a significantly higher rate in duloxetine-treated patients compared to those discontinuing from placebo: dizziness; nausea; headache; paresthesia; vomiting; irritability; and nightmare.

14. After that, the label stayed essentially the same until 2008. In 2008, Lilly took out “trials of up to 9-weeks duration,” changed the percentage withdrawal rate from 2% to 1%, and added additional withdrawal symptoms:

Discontinuation of Treatment with Cymbalta – Discontinuation symptoms have been systematically evaluated in patients taking **duloxetine**. Following abrupt discontinuation in placebo-controlled clinical trials, the following symptoms occurred at a rate greater than or equal to **1%** and at a significantly higher rate in duloxetine-treated patients compared to those discontinuing from placebo dizziness;

nausea; headache; paresthesia; vomiting; irritability; nightmares; **insomnia, diarrhea, anxiety, hyperhidrosis and vertigo.**

15. In 2009, Lilly added “or tapered” to the label as follows (changes are in bold):

Discontinuation of Treatment with Cymbalta – Discontinuation symptoms have been systematically evaluated in patients taking duloxetine. Following abrupt **or tapered** discontinuation in placebo-controlled clinical trials of up to 9-weeks duration, the following symptoms occurred at a rate greater than or equal to 1% and at a significantly higher rate in duloxetine-treated patients compared to those discontinuing from placebo: dizziness; nausea; headache; paresthesia; vomiting; irritability; nightmares; insomnia, diarrhea, anxiety, hyperhidrosis and vertigo.

16. Later in 2009, Lilly added “fatigue” to Cymbalta’s withdrawal effects (changes are in bold):

Discontinuation of Treatment with Cymbalta – Discontinuation symptoms have been systematically evaluated in patients taking duloxetine. Following abrupt or tapered discontinuation in placebo-controlled clinical trials, the following symptoms occurred at a rate greater than or equal to 1% and at a significantly higher rate in duloxetine-treated patients compared to those discontinuing from placebo: dizziness; nausea; headache; **fatigue**; paresthesia; vomiting; irritability; nightmares; insomnia, diarrhea, anxiety, hyperhidrosis and vertigo.

17. In 2012, Lilly changed “at a rate greater than or equal to 1%” to “at 1% or greater,” altered the sequence of the withdrawal side effects and removed “nightmares” so the label read (changes are in bold):

Discontinuation of Treatment with Cymbalta – Discontinuation symptoms have been systematically evaluated in patients taking duloxetine. Following abrupt or tapered discontinuation in placebo-

controlled clinical trials, the following symptoms occurred **at 1% or greater** and at a significantly higher rate in duloxetine-treated patients compared to those discontinuing from placebo: dizziness; **headache**; **nausea**; **diarrhea**; paresthesia; **irritability**; **vomiting**; insomnia, anxiety, hyperhidrosis, and **fatigue**.

18. Since entering the market, Lilly's label for Cymbalta has failed to provide accurate and/or sufficient information about the frequency, severity, and duration of those symptoms caused by stopping the ingestion of Cymbalta (i.e., Cymbalta withdrawal).

19. With regard to frequency of Cymbalta withdrawal, Cymbalta's labeling gives the impression that the likelihood of experiencing withdrawal symptoms is an uncommon side effect. It suggests that the frequency of Cymbalta withdrawal is low, approximately 1%. This characterization, however, is misleading and belied by the clinical data. Lilly's six double-blind placebo controlled clinical trials of Cymbalta, involving a combined total of 1,113 patients, found approximately 44% of users experienced withdrawal symptoms. *See* Exhibit D. In a separate open label clinical trial involving 1,279 patients (discussed in the Perahia article in Exhibit D), approximately 51% of patients experienced withdrawal symptoms. *Id.* As explained in paragraph nine above, the true percentage is likely much higher.

20. With regard to severity of Cymbalta withdrawal, Cymbalta's labeling fails to indicate how severe Cymbalta withdrawal can be. Specifically, in the six

double-blind placebo controlled clinical trials of Cymbalta discussed in Perahia, of the 44% who experienced withdrawal symptoms, 50.6% were moderate and 9.6% were severe. In the larger open-label trial discussed in Perahia, of the 51% of patients experiencing withdrawal symptoms, approximately 46% of were moderate and 17% were severe.

21. With regard to duration of Cymbalta withdrawal, Cymbalta's labeling does not provide any indication of the duration patients can expect to experience withdrawal symptoms following the discontinuation of Cymbalta. In the six double-blind placebo controlled clinical trials of Cymbalta discussed in Perahia, approximately 53.7% of patients experiencing withdrawal symptoms continued to experience symptoms after two weeks. Since the trials did not record withdrawal symptoms after two weeks, there is no indication of how long these remaining patients continued to experience withdrawal symptoms. In the larger open-label trial discussed in Perahia, 55.2% of patients experiencing withdrawal symptoms continued to experience symptoms after two weeks. Similarly, since the open-label trial did not record withdrawal symptoms after two weeks, there is no indication of how long these remaining patients continued to experience withdrawal symptoms. When patients have severe withdrawal reactions coming off antidepressants with short half-lives like Cymbalta, seven or more months may

be required to painstakingly taper off the drug. Lilly's label fails to inform doctors and patients that it can be so difficult to discontinue Cymbalta.

22. Throughout the years, the Cymbalta label also stated that:

During marketing of **other** SSRIs and SNRIs (Serotonin and Norepinephrine Reuptake Inhibitors), there have been **spontaneous** reports of adverse events occurring upon discontinuation of these drugs, particularly when abrupt, including the following: dysphoric mood, irritability, agitation, dizziness, sensory disturbances (e.g., paresthesias such as electric shock sensations), anxiety, confusion, headache, lethargy, emotional lability, insomnia, hypomania, tinnitus, and seizures. **Although these events are generally self-limiting, some have been reported to be severe.**

(emphasis added).

23. Lilly's use of "other SSRIs or SNRIs" is misleading given that adverse events from *Lilly's own clinical trials of Cymbalta* were reported at a rate of between 40 and 50%. Lilly's use of "generally self-limiting" suggests withdrawal is uncommon and that severe reactions are rare. In addition, Lilly's statement that there have been "spontaneous" reports upon discontinuation "during marketing" of these "other SSRIs or SNRIs" misleadingly diverts the reader's attention away from the more reliable adverse events reported *during Lilly's own clinical trials of Cymbalta*. Moreover, a good percentage of the withdrawal events reported in Lilly's controlled clinical trials of Cymbalta were *severe*. This generalized warning, particularly in light of Lilly's clinical trial data on Cymbalta, is plainly misleading.

24. It is worth noting that the FDA's black box and accompanying warnings regarding antidepressant-induced suicidality states that dosage changes, including tapering or stopping the drugs, are among the most vulnerable times for antidepressants to induce suicidal thinking and behavior. Physical symptoms of withdrawal, such as severe nausea, vomiting, disequilibrium, or electric shock-like sensations in the brain can make patients bed-ridden. Lilly's label fails to explain that severe withdrawal reactions can be debilitating or even life-threatening.

25. To a reasonable degree of medical certainty, since Cymbalta's entry onto the U.S. market, in each and every version of the Cymbalta label, Lilly misrepresented or failed to adequately inform prescribing physicians and patients about the frequency, severity, and duration of withdrawal symptoms that can be caused by the discontinuation of Cymbalta.

26. To a reasonable degree of medical certainty, Lilly's label contains material misstatements related to the frequency, severity, and duration of Cymbalta withdrawal. Lilly's misrepresentations and omissions made it impossible for any patient or physician to make an informed decision about the appropriateness of taking or prescribing Cymbalta.

27. Lilly's misleadingly-worded label concerning Cymbalta withdrawal is particularly suspect given that it was Lilly and its paid consultants (prominent psychiatrists) who raised the alarm about antidepressant withdrawal in the 1990s.

During that time period, Lilly was trying to differentiate its antidepressant Prozac as an antidepressant with a long half-life that did not induce withdrawal reactions as frequently as other antidepressants with a short half-life, Paxil in particular.

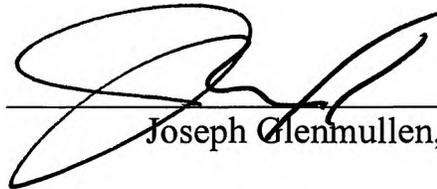
28. Lilly funded a study that compared withdrawal reactions in patients taking Prozac against its competitors at the time, Paxil and Zoloft. *See Rosenbaum et al., Selective Serotonin Reuptake Inhibitor Discontinuation Syndrome: A Randomized Clinical Trial*, 44 *Society of Biological Psychiatry* 77-87 (1998) (attached hereto as Exhibit E). In the study, patients stopped their antidepressants abruptly for five to eight days and were systematically monitored for withdrawal reactions. The conclusion of the study was that Paxil had the highest level of withdrawal, Zoloft to a lesser degree, and there were “few symptoms seen with [Prozac].” The authors reasoned that Prozac did not cause as frequent or severe withdrawal reactions as Paxil and Zoloft because Prozac had a substantially longer half-life than the others.

29. In another article by Rosenbaum and Schatzberg (both paid Lilly consultants), the authors point out that, in patients stopping Effexor (the antidepressant with the shortest half-life), the withdrawal reactions “occur dramatically and commonly.” *See Exhibit C*. Thus, Lilly was aware of the risks associated with antidepressant withdrawal and its relationship to a drug’s half-life. And, Lilly was making antidepressant withdrawal a prominent issue when this was

to its advantage with its earlier drug Prozac. Since Cymbalta's half-life is the second shortest and the closest to Effexor's, Lilly must have recognized that the risk of Cymbalta withdrawal was substantial, as confirmed by its own clinical data (and likely much worse as explained in paragraph nine above). However, rather than being forthcoming about this important risk, Lilly instead chose to obscure the risk by using misleading language in its label once the company was marketing its own antidepressant with an ultra-short half-life, Cymbalta.

I declare, under penalty of perjury, that the information contained herein is true and correct to the best of my knowledge, information, and belief.

Dated this 9<sup>th</sup> day of August, 2013.

  
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Joseph Glenmullen, M. D.