Louis A. Morris, Ph.D.
Expert Report
Cymbalta Discontinuation Litigation

ASSIGNMENT

I have been asked to review documents and associated materials pertaining to cases involving Cymbalta (duloxetine hydrochloride) discontinuation or withdrawal. I have been asked to provide an expert opinion concerning the adequacy of the communication of product information by Eli Lilly and Co. ("Lilly") in its labeling of this product. Between the preparation of this report and the time of trial, I may review additional information and I may form additional or modified opinions based on the materials that I review.

After reviewing materials, to a reasonable degree of professional certainty and based on 40 year of experience at FDA and consulting for the pharmaceutical industry, I believe that product label information presented to physicians and patients about Cymbalta is misleading and inadequate to inform prescribers and patients about the risks of discontinuation.

EDUCATIONAL AND PROFESSIONAL EXPERIENCE

Since January, 2001, I have served as president of Louis A. Morris & Associates, Inc., a regulatory, consulting and research firm for pharmaceutical, health care, advertising and communication companies. In this capacity, I provide advice and research for these companies. I also have an academic position as an adjunct professor at the Temple University School of Pharmacy. My curriculum vita is included as Attachment A.

I received my Ph.D. in Social Psychology from Tulane University in July of 1974. Upon completion of the Ph.D., I worked as a social science research specialist with the U.S. Food and Drug Administration (FDA). During this time and subsequently, I worked on a variety of labeling projects, including the development of class labeling for prescription drugs and revised prescription and over-the-counter drug label formats. I became the Acting Director of FDA's Division of Drug Advertising and Labeling in May of 1986 and held the position until May of 1991. The Division of Drug Advertising and Labeling is currently known as the FDA's Office of Prescription Drug Promotion and was formerly known as the Division of Drug Marketing, Advertising and Communication (DDMAC). I also served as the Chief of the FDA Marketing Practices and Communications Branch from May 1991 to December 1997. As Acting Director and a member of the senior staff of this division, I reviewed prescription drug advertisements directed to health professionals and consumers for compliance with FDA laws and regulations

and developed FDA policy regarding interpretation of drug advertising regulations for emerging forms of promotion (e.g., advertising prescription drugs directly to consumers).

In addition to my work as Division Director and Branch chief in FDA, I participated in a variety of projects directed at communicating the risks of prescription drugs to physicians and patients. I served as head of the "patient labeling project," an FDA-initiative intended to influence private sector organizations and require pharmaceutical manufacturers to disseminate prescription drug information to patients. In this capacity, I reviewed FDA-required patient information for individual prescription drugs for adequacy in the communication of risks, benefits and directions for use and developed policy positions regarding FDA's requirements and/or support of various forms of prescription medicine information including patient package inserts (PPIs), Medication Guides (MGs) and consumer medication information (CMI). As part of my responsibilities at FDA I had primary responsibility for the drafting of the regulations regarding MGs. I also worked on a number of projects regarding the labeling of nonprescription or over-the-counter (OTC) medication. I was designated by FDA as an expert in patient information and education and as described in my CV and I received several awards from FDA for work in this and related areas.

I left FDA to become Senior Vice President of SCP Communications, a post I held from January 1998 to December 2000. This company aided pharmaceutical companies launch new prescription drugs. It published several medical journals, conducted medical education and conducted pre-approval and post-marketing research. I also provided consulting services for prescription and OTC drug manufacturers.

During my years at FDA and after, I have made numerous presentations at professional meetings on the topics of risk communication, testing of drug labels for patient and consumer comprehension, regulation of promotion by FDA and similar topics. I remain active in providing advice to the industry, government and to consumers. Since leaving FDA, my work has required me to keep up-to-date on developments and policies regarding product labeling, drug promotion, risk management and risk communication on FDA-regulated products.

During my career, I have also held numerous teaching positions. I was a Scholar-in-Residence for American University's Marketing Department; part-time instructor at the Johns Hopkins University; part-time lecturer and member of the graduate faculty at the University of Maryland; adjunct faculty member at the Institute for Health Policy Analysis at Georgetown University Medical School and part-time adjunct professor at George Washington University. In this capacity, I taught undergraduate and graduate level courses in Marketing, Consumer Behavior, Advertising, Legal and Regulatory Issues in Marketing and Marketing Ethics.

I have served as an expert consultant for the American Association of Retired Persons, the President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research, National Council on Patient Information and Education, and National Commission on Orphan Diseases. I have also served as a marketing expert for the Federal Trade Commission from February to August of 1991 and for Harvard University's Center for Risk Analysis from July 1995 to December 1997. From November 2002 until January 2006, I served as a member of the FDA's Drug Safety and Risk Management Advisory Committee.

I have served on the editorial board of several journals such as Social Pharmacology, Post Marketing Surveillance, Journal of Public Policy and Marketing, Drug Information Journal, FDA Advertising and Promotion Manual, Oncology and Value in Health.

I have authored numerous scientific papers and book chapters. I have edited one book and authored another on topics related to the labeling of health care products, communication of risk and prescription and OTC drug information to patients and consumers. A complete list of my publications is referenced in my *curriculum vitae.* I charge $600 per hour for consulting fees related to this case. I have testified at deposition and/or in court in the following six (6) cases during the past five (5) years:

• *Raquel Contreras v. Wolters Kluwer Health, et al.,* Case No. DC-07-130. District Court Duval County Texas. , October 14, 2009.

• *Gilberto Hernandez and Ruth Elizondo v. Schering Corp. et al.*, No. 04-L9028 Circuit Court of Cook County, IL., November 18, 2009

• *Bone Care International, LLC and Genzyme Corporation v. Mylan Pharmaceuticals, Anchen Pharmaceuticals and Sandoz, Inc.,* C. A. No. 09-258 (GMS) (Consolidated) (C. A. 10-512 GMS and C.A. 10-429 GMS). United States District Court for the District of Delaware, August 10, 2011 (deposition); November 16, 2011 (court testimony).

• *Abbvie Inc. and Wisconsin Alumni Research Foundation, v. Hospira, Inc.,* C.A. No. 11-648 (GMS), (Consolidated), United States District Court for the District of Delaware, July 9, 2013.

• *Kristin Brown v. Johnson & Johnson and McNeil Consumer Products Company*. Case No. 12-4929, United States District Court for the Eastern District of Pennsylvania, May 2, 2014.

• *Angela Lyles et al v. McNeil-PPC, Inc. et al,* Superior Court of New Jersey – Atlantic County Docket No ALT-L-8655-11, June 25-26, 2014.

MATERIALS REVIEWED

In preparation for forming my opinions in this case, I reviewed documents and materials listed in Attachment B. I also consulted with Dr. Joseph Glenmullen and reviewed his declaration (August 2013). During the discovery process and in the course of preparation for this case, I may review additional materials, including company documents, transcripts of depositions, relevant publications and articles, and other expert reports.

PRESCRIPTION DRUG LABELING

Section 502 of the Food, Drug and Cosmetic Act (FDCA) states that a drug is misbranded if its labeling is false or misleading in any particular. The purpose of a drug label is to provide adequate directions for use of the medication. "Adequate directions for use" means directions under which the layman can use a drug safely for the purposes for which it is intended. Directions for use may be inadequate because, among other reasons, of omission, in whole or in part, or incorrect specification of the conditions for use of the medicine (cf. 21 CFR section 201.5)

Section 201.56 of the FDA regulations provides requirements on content and format of labeling for human prescription drug and biological products. Section (a)(2) states that the labeling must be informative and accurate and neither promotional in tone nor false or misleading in any particular. It also states that labeling must be updated when new information becomes available that causes the labeling to become inaccurate, false, or misleading.

FDA regulations also specify the purpose of prescription drug labeling directed to patients (called Medication Guides). 21 CFR Sec. 208.1(b) states that the purpose of patient labeling for prescription drug products is to provide information when the FDA determines that it is necessary for patients' safe and effective use of the medicine. FDA requires patient labeling when one or more of the following circumstances exists:

(1) The drug product is one for which patient labeling could help prevent serious adverse effects.
(2) The drug product is one that has serious risk(s) (relative to benefits) of which patients should be made aware because information concerning the risk(s) could affect patients' decision to use, or to continue to use, the product.
(3) The drug product is important to health and patient adherence to directions for use is crucial to the drug's effectiveness.

Drug manufacturers are responsible, during drug development and during the post marketing period, to investigate and communicate the risks associated with their products and to

promptly bring those risks to the attention of the FDA, so it can be accurately incorporated in the product labeling to adequately inform physicians and patients.

LABELING OF CYMBALTA FOR DISCONTINUATION SYMPTOMS

[In this section, various revisions of the product label for Cymbalta are discussed. To assure correct reference to the label revisions; the date of the revision specified on the label and/or the date of publication in the Physicians' Desk Reference (PDR) is noted].

FDA approved Cymbalta for the treatment of major depressive disorder in August, 2004. The original label for the product (reprinted in the 2005 PDR) contained a precaution regarding the discontinuation of treatment as follows:

> "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%** (bold emphasis added) and at a significantly higher rate in duloxetine-treated patients compared to those discontinuing from placebo: dizziness; nausea; headache; paresthesia, vomiting; irritability; and nightmare."

This section of the label contained two additional paragraphs that stated that during marketing other SSRIs and SNRIs (drugs in the same or similar pharmacologic class) have spontaneously reported adverse events occurring upon discontinuation; particularly when discontinuation was abrupt. These adverse events included: dysphoric mood, irritability, agitation, dizziness, sensory disturbances (e.g., parasthensias such as electric shock sensations), anxiety, confusion, headache, lethargy, emotional lability, insomnia, hypomania, tinnitus, and seizures. The label noted that although these events are generally self-limiting, some have been reported to be severe. The next paragraph advised readers that patients should be monitored for these symptoms when discontinuing Cymbalta and that that a gradual reduction in dose was suggested when discontinuing the medication. If intolerable symptoms occur during discontinuing treatment, then doctors were advised to consider resuming the original dose and then continue to reduce the dose at a more gradual rate.

The original label advised prescribing physicians that occurrence of symptoms following discontinuation of treatment was relatively uncommon (i.e., "greater than or equal to 2%"). Further, the labeling portrayed this rate as reliable because it was represented that the risk had been "systematically evaluated" in placebo-controlled trials.

There was no information about discontinuation of treatment in the patient counseling information (information for physicians regarding what to tell patients about their treatment) and at that time there was no separate patient information sheet or Medication Guide.

There was additional information for physicians in the Dosage and Administration section of the original label. It repeated information in the precaution section about dosage reduction as follows:

"Discontinuing Cymbalta (duloxetine hydrochloride)

Symptoms associated with discontinuation of Cymbalta and other SSRIs and SNRIs have been reported (see PRECAUTIONS). Patients should be monitored for these symptoms when discontinuing treatment. A gradual reduction in the dose rather than abrupt cessation is recommended whenever possible. If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, the resuming the previously prescribed dose may be considered. Subsequently, the physician may continue decreasing the dose but at a more gradual rate."

There was also some additional information about discontinuation in the Warnings section discussing "Clinical Worsening and Suicide Risk." In this section it noted that:

"If the decision has been made to discontinue treatment, medication should be tapered, as rapidly as is feasible, but with recognition that abrupt discontinuation can be associated with certain symptoms (See Precautions and Dosage and Administration, Discontinuing Cymbalta (duloxetine hydrochloride), for a description of the risks of discontinuation of Cymbalta)."

In a label prepared in June, 2005 reprinted in the 2006 PDR, The precaution about discontinuation of Cymbalta was modified to specify that note that the clinical trials referenced in this section were conducted in patients with "MDD" (major depressive disorder).

There was also a Medication Guide issued. However, the MG focused almost exclusively on the risks of suicidal thoughts and actions in children and teenagers. The MG informed patients, their parents and guardians, that it was important to discuss the all of the risks of treating, or not treating, depression with their healthcare provider, not just the use of antidepressants. Readers were also informed that, besides suicide-related risks, other side effects could occur. They were told to ask their healthcare provider to explain all of the side effects of the prescribed drug and they should ask their healthcare provider or pharmacist where to find more information. The MG did not provide any information about the nature, severity or frequency of symptoms that could occur upon stopping Cymbalta.

In a label prepared in June 2006, reprinted in the 2007 PDR, the labeling for Cymbalta was revised. However, information related to discontinuation was not modified.

In a label prepared in June 2007, reprinted in the 2008 PDR, the information about discontinuation in the Precautions section of the label was revised; omitting reference to "MDD" when describing the trials. The rate and list of symptoms that occurred following abrupt discontinuation was revised as follows:

"Following abrupt discontinuation in placebo-controlled trials, the following symptoms occurred at a rate **greater or equal to 1%** ((bold emphasis added) 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."

Thus, the June 2007 version of the Cymbalta label revised the list of side effects that could occur following discontinuation but described the rate as occurring, again, at a low "greater or equal to 1%". Again, the label represented that these side effects of discontinuation were uncommon.

The June 2007 label also modified the information included in the Information for Patients section and added a revised MG for patients. However, the new information and the MG again focused extensively on the increased risk of suicide with antidepressant medication. The heading for the section discussing benefits and risks was changed to read; "What else do I need to know about antidepressant medicines?" (Rather than focusing on benefits and risks), however, the statement about discussing the risks of treatment remained in the document. The MG contained a statement (the last section entitled "What else do I need to know about antidepressant medicines?") that stated:

"Never stop an antidepressant without first talking to a healthcare provider. Stopping an antidepressant medicine suddenly can cause other symptoms."

There was no change in the Dosage and Administration section or the section in the Warnings section discussing tapering the dose.

In the June, 2008 revision of the label, reprinted in the 2009 PDR, the label for Cymbalta was revised using a newly instituted label format change. However, the information presented in the label remained the similar. In the Highlights section of the new label, there was a notation to a revised change regarding discontinuation in 2007 label (see "Recent Major Changes") already noted in the June 2007 label and there was a sentence included in the Highlights section under "Warnings and Precautions" noting;

"Discontinuation: May result in symptoms including dizziness, nausea, headache, fatigue, paresthesia, vomiting, irritability, nightmares, insomnia, diarrhea, anxiety, hyperhidrosis, and vertigo."

The information in the Precautions section was revised to note that the discontinuation systematically studied in the placebo-controlled trials followed abrupt "or tapered" discontinuation. However, the rate of side effects remained at "**greater than or equal to 1%**." (bold emphasis added) . Other information about the types of side effects that occurred and advice about tapering the dosage remained the same as the previous label revision. The Information for Patients section was revised in a new format and entitled "Patient Counseling Information." Healthcare professionals were informed to discuss the benefits and risks of Cymbalta therapy with patients, their families and caregivers and advise them to read the MG. However, there was no specific information included in this section about discontinuation. The MG contained the same information as in the previous version noting to never stop taking an antidepressant without first talking to a healthcare provider.

The information included in the Dosage and Administration section was reduced and summarized to state that:

"Discontinuing Cymbalta
Symptoms associated with discontinuation of Cymbalta and other SSRIs and SNRIs have been reported. A gradual reduction in the dose rather than abrupt cessation is recommended whenever possible (*see Warnings and Precautions).*"

I could not find any meaningful change regarding discontinuation of Cymbalta in the February, 2009 label revision, reprinted in the 2010 PDR, or in the March, 2010 version, reprinted in the 2011 PDR. In the 2010 version, the list of symptoms that could occur during discontinuation was revised slightly in the Highlights and Warnings and Precautions section as follows:

"Discontinuation: May result in symptoms including dizziness, nausea, headache, paresthesia, fatigue, vomiting, irritability, insomnia, diarrhea, anxiety, hyperhidrosis, and vertigo" (deleting "nightmares" and "vertigo" from the list).

In addition the description of the rate of occurrence of side effects was modified to read that the symptoms occurred at a rate of "**1% or greater**" (bold emphasis added) as opposed to a rate of "**greater or equal to 1%**" (bold emphasis added) in previous versions of the label.

The May 2011 version, reprinted in the 2012 PDR, also revised the list of symptoms that may occur following discontinuation as follows (changing the order of symptoms):

> "Discontinuation: May result in symptoms including dizziness, nausea, headache, paresthesia, fatigue, vomiting, irritability, insomnia, diarrhea, anxiety, and hyperhidrosis."

RATE OF DISCONTINUATION SYMPTOMS

Although the Cymbalta product label states that "the [following] symptoms occurred at a 1% or greater rate"; the rate of symptom occurrence appears to be much higher. Combining data from 6 short term clinical trials in which treatment was stopped abruptly, Perahia, Kajdasz, Desaiah and Haddad (2005) found that discontinuation emergent adverse events occurred at a rate of 44% for Cymbalta patients compared to 23% for placebo patients (i.e., the percent of patients that reported at least one adverse event following discontinuation). The severity of the side effects in the Perahia et al. analysis was categorized by the authors as; mild (40%), moderate (51%) or severe (10 %).

A longer term, 34-week placebo controlled trial, found the rate patients experiencing at least one discontinuation emergent adverse event to be 9%. The severity of the side effects in this study were categorized by the authors as; mild (71%), moderate (27%) or severe (3%). In 52-week open-label study (a study in which patients knew that they were taking an active drug whereas in most placebo-controlled trials patients are "blinded" and not told whether they are taking an active medicine or a placebo), the rate of discontinuation emergent adverse events was 51%. The severity of the side effects in this study was categorized by the authors as; mild (37%), moderate (46%) or severe (17 %).

INTERPRETATION OF DISCONTINUATION RATE

Over the years the label for Cymbalta has been revised numerous times. The nature and order of symptoms that could occur when Cymbalta is discontinued have been revised consistently. However, the basic message about the frequency of discontinuation symptoms has remained consistent. Readers of the recent (November 2011) Cymbalta label are informed that:

> "Following abrupt or tapered discontinuation in placebo-controlled clinical trials the following symptoms occurred at **1% or greater** (bold emphasis added) and at a significantly higher rate in duloxetine-treated patients compared to those discontinuing from placebo: dizziness, nausea, headache, paresthesia, fatigue, vomiting, irritability, insomnia, diarrhea, anxiety and hyperhidrosis"

However, the article by Perahia, Kajdasz, Desaiah and Haddad (2005) shows that the rate of side effects following discontinuation was 44% (i.e., the percentage of patients in clinical trials that experienced an adverse event).

The interpretation of the phrase "1% or greater" is dependent on the "context" in which the phrase appears (cf., Barsalou, 1982; Gennari, MacDonald, Postle and Seidenberg, 2007). The context for the phrase "1% or greater" is a prior phrase in the sentence noting "the following symptoms occurred". A reader would interpret the phrase "the following symptoms occurred" to mean that in aggregate, the following symptoms occurred, not that "each" of the following symptoms occurred. If the manufacturer had intended that the reader should interpret the "1% or greater" to mean the rate for any one of the following symptoms, the phrase should have been more explicit (e.g., "each" of the following symptoms occurred at a 1% or greater rate), thereby adding the proper context to convey this meaning. As it stands, the description of the rate of discontinuation symptoms in the Cymbalta label is misleading.

It is important to note that the incidence rate of adverse reactions *to taking the drug, not to discontinuing the drug,* is described in the Adverse Reactions section of the label. However, there is much greater context given in this section and the reader can correctly interpret that the percentages provided apply to the incidence of individual side effects. For example, in the section on "clinical trial data sources" (section 6.1 of the 2011 label) it states that;

> "The stated frequencies of adverse reactions represent the proportion of individuals who experienced, at least once, a treatment-emergent adverse reaction of the type listed."

The phrase "of the type listed" makes it clear that the frequencies listed are meant to apply to specific individual side effects, not side effects in the aggregate. Further, when examining the rates of side effects in the trials (sections 6.4 and 6.5) there is a listing of individual side effects presented in the Tables (see Tables 2 and 3). The phrases "5% or more" and "2% or more" are presented in the heading for these tables. However, unlike the description of *discontinuation* side effects, where there is no additional context given for this phrase, in the Adverse Reactions section, the tables present a listing of individual side effects that occur when taking the drug and the percentage of patients reporting these individual treatment emergent adverse reactions. It is clear that the percentage shown in these tables applies to individual side effects and is not meant to convey an aggregate percentage of patients experiencing any one of the side effects.

LABELING OF CYMBALTA FOR DEPENDENCY AND WITHDRAWAL

The originally approved label for Cymbalta and subsequent label revisions contained a section describing Drug Abuse and Dependency. The section stated that Cymbalta was not a

controlled substance and that there was no indication for drug-seeking behavior in clinical trials (although the drug had not been systematically studied for abuse potential). Physicians were informed, nevertheless, to follow patients closely for signs of misuse or abuse (development of tolerance, incrementation of dose and drug seeking behavior). The information provided in this section did not change in the revised versions of the label over the subsequent years.

Dr. Joseph Glenmullen, a psychiatrist who also serves as an expert in this matter, has stated that Cymbalta causes withdrawal symptoms. He cites his own publications, pharmacologic properties (half-life) data, and clinical review data from the Perahia et al. study to support his views (see Glenmullen report). However, there was no information provided in the label mentioning withdrawal per se.

Readers of the product label are informed in the section 5.1 "Clinical Worsening and Suicide Risk" that when discontinuing treatment: "medication should be tapered, as rapidly as is feasible, but with recognition that abrupt discontinuation can be associated with certain symptoms."Other sections of the label also mention tapering patients off the medicine and describe side effects of discontinuation. However, there are no dosage directions provided about how to gradually reduce the dose (time and dose schedule) to minimize or prevent withdrawal or discontinuation-emergent symptoms.

It is possible that physicians or patients may seek information about Cymbalta and its effects upon discontinuation from sources other than the product label. However, it is important to note that the labeling of prescription medicines not only directly conveys information to healthcare providers and patients via the approved package insert and MG but the approved label also controls the content of advertising and promotional material. To be considered truthful (and not false or misleading) Lilly is, and always has been, required to disseminate promotional materials that are consistent with information in the approved label. When reviewing advertisements and promotional labeling pieces, FDA uses the approved label to determine if the disseminated information is truthful. Therefore, it would be left to physicians to talk to knowledgeable colleagues or review the medical literature to obtain information about Cymbalta withdrawal effects that went beyond the information presented in the product label. As most physicians would be likely to consider the labeling as correct and accurate, they would not know (unless they had come across previous research) that there were altering opinions and data to support the view that withdrawal effects could occur when stopping Cymbalta.

INSTITUTE OF SAFE MEDICICATION PRACTICES (ISMP) REPORT ON CYMBALTA

According to their website (ISMP, 2014); ISMP "is a nonprofit organization devoted entirely to medication error prevention and safe medication use. ISMP represents over 35 years

of experience in helping healthcare practitioners keep patients safe, and continues to lead efforts to improve the medication use process. The organization is known and respected worldwide as the premier resource for impartial, timely, and accurate medication safety information."

They disseminate a newsletter (called "QuarterWatch") that monitors FDA-reported adverse events and provide analysis regarding these events. In the October 3, 2012 issue, ISMP reported on Cymbalta and "Serious Withdrawal Symptoms." The report stated that in the first quarter of 2012, FDA received 48 case reports of drug withdrawal identifying Cymbalta as the suspect medicine. Investigating FDA safety reviews, ISMP noted that there was a lack of concern regarding discontinuation symptoms by FDA. ISMP quoted an FDA review as stating: "It appears that symptoms are relatively mild and reliably predictable for a significant minority of patients. Tapering duloxetine at discontinuation appears to be advisable for optimal patient comfort, but not tapering does not appear to pose any serious risk."

ISMP then reviewed withdrawal reports in the Peripha et al. paper and noted that 44% of patients reported symptoms after abrupt withdrawal after 8 or 9 weeks of treatment; with about 10% of these symptoms rated as "severe" and 54% lasted more than one or two weeks. ISMP noted that the MG informs patients to talk to their healthcare provider about stopping antidepressant medication. However, ISMP concluded that the information for physicians was inadequate regarding discontinuation. ISMP noted that although the most common discontinuation problems were listed in the label, there was insufficient information provided to physicians about how to taper off the medicine and that withdrawal problems are not included in the topics enumerated in the Patient Counseling section informing physicians what to discuss with patients.

The ISMP report concluded that "a major lapse has occurred in the FDA-approved information for patients about the risks of stopping duloxetine." They also stated that although the information for physicians was somewhat better, it was still inadequate in terms of what topics to counsel patients about and there was no information provided about how to taper patients off the drug.

EMA INFORMATION ABOUT TREATMENT DISCONTINUATION

The European Medicines Agency (EMA) regulates the review and approval of new medication marketed in the European Union (EU). As part of their review of new drug applications, they review and approve a "Summary of Product Characteristics" (SmPC) for each new medication. The SmPC describes the properties and the officially approved conditions of use of a medicine. Summaries of product characteristics form the basis of information for healthcare professionals on how to use the medicine safely and effectively (EMA, 2014)

The information about Cymbalta discontinuation in the SmPC is quite different than the information in the approved US product label. The SmPC for Cymbalta states the following:

> *"Discontinuation of treatment*
> Withdrawal symptoms when treatment is discontinued are common, particularly if discontinuation is abrupt (see section 4.8). In clinical trials adverse events seen on abrupt treatment discontinuation occurred in approximately 45% of patients treated with Cymbalta and 23% of patients taking placebo. The risk of withdrawal symptoms seen with SSRI's and SNRI's may be dependent on several factors including the duration and dose of therapy and the rate of dose reduction. The most commonly reported reactions are listed in section 4.8. Generally these symptoms are mild to moderate, however, in some patients they may be severe in intensity. They usually occur within the first few days of discontinuing treatment, but there have been very rare reports of such symptoms in patients who have inadvertently missed a dose. Generally these symptoms are self-limiting and usually resolve within 2 weeks, though in some individuals they may be prolonged (2-3 months or more). It is therefore advised that duloxetine should be gradually tapered when discontinuing treatment over a period of no less than 2 weeks, according to the patient's needs (see section 4.2)."

There are clear differences between the EU information and the US product information. The EU SmPC notes:

- discontinuation results in withdrawal effects
- withdrawal symptoms are common, particularly with abrupt discontinuation
- discontinuation symptom occurs in 45% of patients
- in some patients withdrawal symptoms may be severe in intensity
- symptoms are usually self-limiting (resolving within 2 weeks); however for some these symptoms may be prolonged (2-3 months or longer).
- dose tapering over a period of no less than 2 weeks, according to patient's need.

The content and implications of the EU description is starkly different than the US product information. The EU SmPC clearly views discontinuation symptoms as withdrawal effects that are common (45% of patients). It informs physicians that some patients may have severe and persistent (2-3 months of longer) symptoms and there is more information provided about dose tapering in another section of the SmPC (see section 4.2) stating:

> *"Discontinuation of treatment*
> Abrupt discontinuation should be avoided. When stopping treatment with Cymbalta the dose should be gradually reduced over a period of at least one to two weeks in order to reduce the risk of withdrawal reactions (see sections 4.4 and 4.8). If intolerable symptoms

occur following a decrease in the dose or upon discontinuation of treatment, then resuming the previously prescribed dose may be considered. Subsequently, the physician may continue decreasing the dose, but at a more gradual rate."

Section 4.8 of the SmPC describes "Undesirable Effects" of Cymbalta. Section c describes "selected adverse reactions" related to discontinuation of treatment as follows:

"Discontinuation of duloxetine (particularly when abrupt) commonly leads to withdrawal symptoms. Dizziness, sensory disturbances (including paraesthesia or electric shock-like sensations, particularly in the head), sleep disturbances (including insomnia and intense dreams), fatigue, somnolence, agitation or anxiety, nausea and/or vomiting, tremor, headache, myalgia, irritability, diarrhoea, hyperhydrosis and vertigo are the most commonly reported reactions.

Generally, for SSRIs and SNRIs, these events are mild to moderate and self-limiting, however, in some patients they may be severe and/or prolonged. It is therefore advised that when duloxetine treatment is no longer required, gradual discontinuation by dose tapering should be carried out (see sections 4.2 and 4.4)."

CONCLUSION

Based upon my experience at FDA and consulting for the pharmaceutical industry, and based upon my review of the materials , my opinion to a reasonable degree of professional certainty is that the information presented to physicians and patients about Cymbalta is misleading and inadequate to inform prescribers and patients about the risks of discontinuation. Although the most common side effects are presented in the US product label, the frequency and/or severity of the withdrawal symptoms are not fully or accurately communicated. The frequency of discontinuation side effect occurrence stated in the product information is misleading and conveys a much lower rate than described in other publications and reports; including product information approved for drugs marketed in the European Union. Patients are not adequately informed about the severity or frequency of discontinuation side effects and are told only to discuss stopping the medicine with their doctor.

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

9/18/14
Date

Louis A Morris
Louis A. Morris, Ph. D.

Attachment A

CURRICULUM VITAE

LOUIS ALLEN MORRIS

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EDUCATION

B.A. Boston University (1968)

M.A. New School for Social Research (1971)

Ph.D. Tulane University (1974) (Major: Social Psychology)

CURRENT POSITION

President, Louis A. Morris & Associates, Inc.

PREVIOUS POSITIONS

Social Science Research Specialist, Office of Biometrics and Epidemiology, Food and Drug Administration, Rockville, Maryland, July, 1974 - August, 1976

Director, Prescription Drug Labeling Project, Food and Drug Administration, Rockville, Maryland, August, 1976 - January, 1981

Chief, Drug Research, Education and Labeling Branch, Food and Drug Administration, Rockville, Maryland, January, 1981 - May, 1991

Acting Director (rotation), Division of Drug Advertising and Labeling, May, 1986 - May, 1991

Chief, Marketing Practices and Communications Branch, (HFD-40), Food and Drug Administration, May, 1991 - December, 1997

Senior Vice President, SCP Communications. January 1998 – December, 2000

UNIVERSITY APPOINTMENTS

Scholar-in-Residence, American University, Marketing Department, January, September, 1988 – December, 1997

Instructor in Marketing (part-time), Johns Hopkins University, Department of Administrative Science and Business, Baltimore, Maryland, October, 1982 - May, 1990

Assistant Professor (Lecturer) (part-time), member of graduate faculty, University of Maryland, College Park, Maryland, August, 1978 - 1991; September, 1997 - December, 1997

Adjunct Faculty, Institute for Health Policy Analysis, Georgetown University Medical School, Washington, DC. July 1988 - January 1990

Adjunct Professor (part-time), George Washington University, Washington, D.C., May, 1997 – December, 1997

Adjunct Associate Professor, Temple University School of Pharmacy, Philadelphia, PA, December, 2001 – Present

BOOKS AND EDITED VOLUMES

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PAPERS, INVITED ADDRESSES

Over 600 presentations at national and international forums. Invited column in Pharmaceutical Executive: "Direct-from-Lou," June, 1999 – 2009.

HONORS AND AWARDS

National Science Foundation Science Development Fellowship, September 1972 - May 1974

FDA Commendable Service Award, June, 1979

Visiting Scholar - University of Missouri - Kansas Medical School, Sisters of St. Mary's Hospital, February, 1983

Visiting Scholar - University of Wisconsin - Department of Administrative Pharmacy - Madison, Wisconsin - April, 1997

Visiting Scholar - University of Minnesota - Department of Administrative Pharmacy – Minneapolis, Minnesota - May, 1999

FDA Group Recognition Awards:
May, 1992 - Naproxin Investigation
May, 1995 - Pharmacoeconomics Team
May, 1996 - Comparative Treatments Conference
May, 1997 - Advertising (Commendable Service Award)
May, 1998 - OTC Labeling

FDA Commissioner's Special Citation:
May, 1994 - Patient Information Project

February, 1997 - Medication Guides
February, 1997 - OTC Label Formats

Expert Promotion - FDA, May, 1993

Award of Merit - FDA, May, 1994

FDA Distinguished Career Award - December, 1997

CDER Career Service Award - December, 1997

Outstanding Teacher - Adjunct, Kogod School of Business Administration, American University - March, 1994

Outstanding Service - Drug Information Association, June, 1997

EXPERT CONSULTANTSHIPS

American Association of Retired Persons

President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research

National Council on Patient Information and Education

National Commission on Orphan Diseases

Social Pharmacology (editorial board)

Post Marketing Surveillance (editorial board)

Journal of Public Policy and Marketing (editorial board)

Drug Information Journal (editorial board)

FDA Advertising and Promotion Manual (editorial board)

Oncology (editorial board - regulatory affairs editor)

InTouch (editorial board - patient affairs editor)

Value in Health (editorial board)

Federal Trade Commission, Marketing Expert, Washington, DC (part-time detail), February, 1991 - August, 1991

Harvard University's Center for Risk Analysis, July, 1995 - December, 1997.

Food and Drug Administration, Expert Consultant, Rockville, MD, March, 1998 – 2006

Food and Drug Administration, member of the Drug Safety and Risk Management Advisory committee, November, 2002 – 2006.

Numerous Pharmaceutical, Advertising, and Health Communications Companies and Attorneys.

PROFESSIONAL AFFILIATIONS

Association for Consumer Research
(Advisory Council 1982-1984)

American Marketing Association
(member 1988-1995)

Drug Information Association
(Board of Directors 1992 - 1996)
(President 1994-1995)

International Society of Pharmacoeconomics and Outcomes Research
(Health Policy Development Committee – 1998-2002)

American Association for the Advancement of Science, 2009 – present)

CONFERENCES ORGANIZED

Symposium on Patient Package Inserts, Washington, DC, November, 1976 (proceedings published - Drug Information Association Journal)

Product Labeling and Health Risks, Cold Spring Harbor, NY, May, 1980 (proceedings published - Cold Spring Harbor Laboratories)

New Directions in Patient Communications, Williamsburg, VA, March, 1983

Educating Patients, 1984 - The Practitioner's Perspective, Washington, DC, June, 1984 (program chairman)

Patient Information and Education, Drug Information Association, Washington, DC, November, 1992 (program co-chairman)

Regulatory Issues in Quality of Life, Drug Information Association, Washington, DC, January, 1994 (program co-chairman)

Comparing Treatments: Safety, Effectiveness and Cost-Effectiveness, Food and Drug Administration, Bethesda, MD, March, 1995.

Drug Information Association – Internet Conference, Washington, DC, October, 1999.

Merging Marketing and Clinical Development, Drug Information Association, Philadelphia, PA. March, 2001 and March 2002.

New Initiatives in Risk Management, Drug Information Association, Philadelphia, PA. April, 2001 and April 2002.

Attachment B

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June, 2005 (reprinted in the 2006 PDR)
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