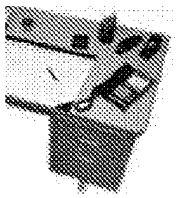
**Carol H Stephens/AM/LLY@LILLY**
09/17/2006 04:02 PM

To Michael Detke/AM/LLY@Lilly
cc Ann Robbins Sakai/AM/LLY@Lilly, BROPHY_GREGORY_T@LILLY.COM, EGGERS_MATT@LILLY.COM, Fujun Wang/AM/LLY@Lilly, James M Russell/AM/LLY@Lilly, Lisa A Vierhile/AM/LLY@Lilly, Richard Bump/AM/LLY@Lilly, WERNICKE_JOACHIM@LILLY.COM
bcc
Subject Re: Fw: Follow-up on the PLR meeting - tapering

The sentence has been struck through. Thanks to all.
Regards, Carol
Regulatory Affairs Global Labeling
Phone 317.276.1446 Fax 317.433.6771

Michael Detke/AM/LLY



**Michael Detke /AM/LLY**
09/15/2006 01:07 PM

To Ann Robbins Sakai/AM/LLY@Lilly, James M Russell/AM/LLY@Lilly, WERNICKE_JOACHIM@LILLY.COM@Lilly
cc Carol H Stephens/AM/LLY@Lilly, Fujun Wang/AM/LLY@Lilly, Richard Bump/AM/LLY@Lilly, BROPHY_GREGORY_T@LILLY.COM, Lisa A Vierhile/AM/LLY@Lilly, EGGERS_MATT@LILLY.COM
Subject Re: Fw: Follow-up on the PLR meeting - tapering

My proposal is that we plan to delete the sentence struck through below. Overall, it strongly implies that tapering substantially improves tolerability, which does not represent the data accurately. To Rick's point, it (perhaps more weakly) implies that tapering solves all tolerability problems entirely, which would be an even worse misinterpretation of the actual data. To Greg's point today, the last paragraph, second sentence still indicates that tapering is recommended, and is inconsistent, but I would not recommend removing it now because 1) it's from previous class labelling and not worth the fight, and more importantly 2) it may still help patients to taper and almost certainly won't hurt them in the vast majority of clinical situations (one can always think of rare exceptions, such as needing to be started quickly on an MAOI, but these shouldn't drive our decision).

Process-wise, this sentence was added in the GAD submission, so we'll have to deal with that in the GAD label negotiations, but I'd rather do that than mislead patients/prescribers.

Joe, Jim, Ann, please reply with agreement or not. Thanks.

Mike

### 5.9 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 10-weeks duration, the following symptoms occurred at a rate greater than or equal to 2% and at a significantly higher rate in either the MDD or GAD Cymbalta-treated patients compared to those discontinuing from placebo: dizziness; nausea; headache; paresthesia; vomiting; irritability; and nightmare. ~~When patients were tapered over 2 weeks after acute treatment in 9- or 10-week GAD studies, no adverse events met criteria as described above.~~

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.

Patients should be monitored for these symptoms when discontinuing treatment with Cymbalta. 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, then resuming the previously prescribed dose may be considered. Subsequently, the physician may continue decreasing the dose but at a more gradual rate (add reference to dosing 2.X).

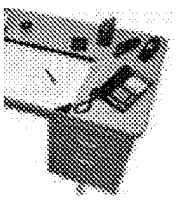
---

Michael J. Detke, M.D., Ph.D.
Cymbalta & Prozac Global Medical Director
Lilly Research Laboratories
+1-317-277-6420



Co-marketing statement:
1) We are sharing this information only for the purposes of co-promoting duloxetine in those regions of the world where Lilly & BI are co-promotion partners.
2) It is not to be shared to influence or direct how BI markets its brand of duloxetine in co-marketing regions.
3) It should not be considered a final determination of Lilly's brand strategy in regions where Lilly & BI are co-marketing competitors.

Ann Robbins Sakai/AM/LLY



**Ann Robbins Sakai /AM/**LLY
09/15/2006 12:30 PM

To Carol H Stephens/AM/LLY@Lilly
cc Joachim Wernicke/AM/LLY@Lilly, Michael Detke/AM/LLY@Lilly, Richard Bump/AM/LLY@Lilly, Fujun Wang/AM/LLY@Lilly
Subject Re: Fw: Follow-up on the PLR meeting

Carol you neglected to copy Rick on your note below

Rick,
Mike did represent the points you make below at the meeting this morning and is going to follow up with both you and Jim Russell (since the same language is in the GAD sNDA draft label) to make a final decision on what to do with this language. The core PLR team will then adopt your joint medical decision. Thanks, Ann

Ann R. Sakai, PhD.
Regulatory Advisor
Desk Phone: 317-651-5642
Cell Phone: 317-529-2569
Fax: 317-276-1652
email: sakai_ann_robbins@lilly.com

Carol H Stephens/AM/LLY

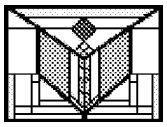
**Carol H Stephens /AM/LLY**
09/15/2006 10:42 AM

To Joachim Wernicke/AM/LLY@Lilly, Carol H Stephens/AM/LLY@Lilly, Ann Robbins Sakai/AM/LLY@Lilly, Michael Detke/AM/LLY@Lilly
cc
Subject Fw: Follow-up on the PLR meeting

Rick -- I believe Mike is going to follow up with you on this.

All -- here is Rick's response.
Regards, Carol
Regulatory Affairs Global Labeling
Phone 317.276.1446 Fax 317.433.6771

------ Forwarded by Carol H Stephens/AM/LLY on 09/15/2006 10:41 AM ------



**Richard Bump /AM/LLY**
09/15/2006 09:45 AM

To Carol H Stephens/AM/LLY@Lilly
cc
Subject Re: Follow-up on the PLR meeting

Dear Fugan and all,

My point was not so much what events should be included, but concern that the implication from the wording is that tapering eliminates the risk of discontinuation symptoms. None of the individual studies specifically designed to look at this (SUI or GAD) have shown a benefit to tapere compare with abrupt discontinuation. I just believe the sentence that concludes the first paragraph is not accurately reflecting the lack of benefit (or lack thereof) of tapering in studies designed to look at this specifically.

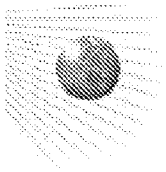
Rick

Carol H Stephens

**From:** Carol H Stephens
**Sent:** 09/15/2006 08:51 AM
**To:** Richard Bump
**Subject:** Fw: Follow-up on the PLR meeting

Here is Fujun's response. Mike is going to confer with you about it.
Regards, Carol
Regulatory Affairs Global Labeling
Phone 317.276.1446 Fax 317.433.6771

----- Forwarded by Carol H Stephens/AM/LLY on 09/15/2006 08:45 AM -----



Fujun Wang /AM/LLY
09/14/2006 05:38 PM

To Joachim Wernicke/AM/LLY@Lilly, Carol H Stephens/AM/LLY@Lilly, Ann Robbins Sakai/AM/LLY@Lilly
cc Maurice Lunik/AM/LLY@Lilly
Subject Follow-up on the PLR meeting

Hi,

Here is the my follow-up for the questions raised in today's PLR meeting:

1. Section 5.8 Discontinuation of Treatment with Cymbalta

Rick's question: Should Dizziness be included as taper -emergent AE?

Response: No event met the criteria . What Rick looked at was the report for HMBR only (Table 2.7.4.1.11). The table should be used is Table 2.7.4.1.10 (this table pooled all CAD studied with taper phase).

2. Duration data for Overall duloxetine database for Joe to draft some language in section 6.8

Here is the report (look at the last page for all indications )

Joe: If we want to make changes in that section , we could mention that the frequencies were determined based on all duloxetine -treated patients in all duloxetine clinical trials .

FQEXPGG1.doc

Let me know if you need other info .

Fujun