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From: Macfadden, Wayne

Sent: Wednesday, November 16, 2005 3:34 AM

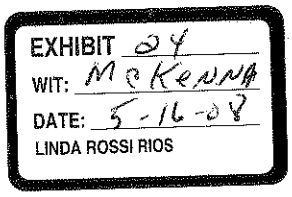
To: Block, Gilbert; Bradley, Kathryn

Cc: McKenna, Kevin; Horowitz, Gary; Martino, Marie; Beamish, Don G;

Scott, Mark S (Wilmington); Brecher, Martin

Subject: RE: Review of draft US Prescribing Information prior to the

Rockville Meeting



Gil,

not sure if you'll be calling in tomorrow, but wanted to update you & others on some of the discussions the submission team has had here:

- we've agreed to drop the term bimodal. However we do reference SQL's 'mood stabilizing properties' in the clin pharm section when we note its efficacy in both bipolar mania & depression. This is slightly different, we think, then attempting to charactize it as a "mood stabilizer" a term the FDA is not keen on. In any event, the team was interested in testing the waters with the FDA now that we have the unique feature of efficacy in mania & depression

- re: the reduction of suicidality. Both of our consultants (Leber & Montgomery) were encouraging in the discussion of whether or not to describe this feature in the label, despite not having pre-specified it as an endpoint of interest to the FDA . Our current view is to note this as a feature of SQL's efficacy, distinct from SQL's apparent absence of rx- emergent suicidality.

re: the concern of cherry- picking; the matter of reducing suicidality is perhaps the most important treatment goal in pts with depression of any kind. To the best of my knowledge, no agent for the treatment of bipolar disorder since Lithium has been shown to reduce suicidality. Lastly, the incidence of suicide is higher in bipolar disorder than in most other mental disorders. So, there is sufficient import, both clinically & from a public health standpoint to report a finding that suggests reduction in suicidal thinking in this population.

That said, we realize the data are not overwhelming and there is not a high likelihood of the acceptance by the FDA of this language. The team's consensus, however, is to proceed, as we believe we a) pass the red- face test and are not making an unreasonable request of the FDA , b) are not trying to force any other data from any other secondary endoint in the label and c) describing this in the label would be a major area of differentiation from other compounds used to treat bipolar d/o.

(Kevin: pls correct me if I misrepresented the discussion)

regards

Wayne

-----Original Message-----

From: Block, Gilbert

Sent: Saturday, November 12, 2005 1:39 PM

To: Bradley, Kathryn

Cc: McKenna, Kevin; Horowitz, Gary; Martino, Marie; Beamish, Don G; Scott, Mark S (Wilmington); Macfadden, Wayne; Brecher, Martin

Subject: FW: Review of draft US Prescribing Information prior to the Rockville Meeting

Importance: High

Kathy,

Please see my suggested changes in the proposed label indicated in revision marks. The most problematic issues are as follows:

1) use of the term bimodal- i do not agree with this from either a pharmacologic ro statistical point.

2) focus on reduction of suicidal ideation vs placebo with madrs 10- i have difficulty cherry- picking this out, especially after review of the columbia analysis. although not optimal, the team might consider modifying the conclusion from the columbia analysis and talk about " no evidence of increased risk of suicidal behavior or ideation in the two pivotal trials at doses of 300 mg and 600 mg in patients with bipolar depression". This may be problematic given the black box re: depression but I have attempted to obviate this by the proposed wording.

In the dosing section, it is likely that the division may have an issue with describing the dosing titration for the 600 mg group as we state that there is no additional benefit. A safer course to take would be to put the tiration regimen for both the 300 and 600 mg groups in the description of the clinical studies and only keep the titraiton regimen up to 300 mg in the dosing section (where we refer to the clinci studies section anyway).

I will call in on monday morning when the team speaks with Montgomery and Leber and will be available after that if needed.

Gil

-----Original Message-----

From: Bradley, Kathryn

Sent: Monday, November 07, 2005 3:55 PM

To: McKenna, Kevin; Horowitz, Gary; Martino, Marie; Block, Gilbert;

Beamish, Don G; Scott, Mark S (Wilmington)

Subject: Review of draft US Prescribing Information prior to the

Rockville Meeting

The labeling team would like you to review the draft label and provide any comments to me prior to the Rockville meeting. This will also help me to answer questions from the larger group in Rockville. If you make suggestions to the label, could you please provide me with you rationale so that I can share it with the team. The next US labeling team is scheduled for Thursday and I would appreciate your feedback for this meeting.

Please note the changes in the Clinical Pharmacology section using the word "bimodal" The team realizes this is a risk and would like your opinion. Also, the text around EPS still is in progress. Lastly, I have made notes in red in each section that will be used for annotations.

Thank you

Kathy

Kathryn Bradley

Regulatory Affairs-Labeling

Neuroscience Brands

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