

From: Arnold, Barry DC
Sent: Tuesday, July 17, 2001 1:43 PM
To: Geller, Wayne
Cc: Dev, Vikram J
Subject: RE: Weight gain and CPI Justification document
Wayne,

Please start with Stefan. If he is not available, please ask Janet Spiers to explore this on your behalf.

Best regards,

Barry

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

From: Geller, Wayne
Sent: 17 July 2001 13:42
To: Arnold, Barry DC
Cc: Dev, Vikram J
Subject: RE: Weight gain and CPI Justification document

Dear Barry,

Thanks for your prompt response. As you suggest, I would like to confirm the signoff for both the CDS and JD immediately. Should I contact Stefan Carlsson or someone else to verify this? I will get back to you once this has been established.

Best regards,
Wayne

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

From: Arnold, Barry DC
Sent: Tuesday, July 17, 2001 3:58 AM
To: Geller, Wayne
Cc: Dev, Vikram J
Subject: RE: Weight gain and CPI Justification document

Wayne,

Many thanks for the information which causes me great concern. We can take this forward two ways:

1. I call Martin and clarify his rationale for the delay.
2. You, me, Vikram and martin have a video/teleconference to discuss the acceptability of this.

Whatever, I would be grateful if you could confirm that the amended CDS and the JD were signed off in line with the SERM process. If they were, then we have significant issue with commercial blocking this. If so, I will then talk to Bill Bastain, the relevant TA Director, and also raise the matter at GCLT - we cannot have Commercial interfering with clinical justified labelling decisions.

Best regards,

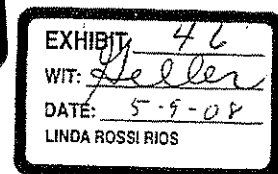
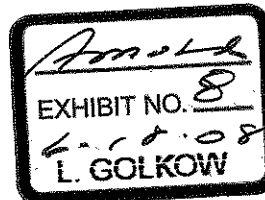
Barry

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

From: Geller, Wayne
Sent: 16 July 2001 16:21
To: Arnold, Barry DC
Cc: Dev, Vikram J
Subject: FW: Weight gain and CPI Justification document

Dear Barry,

Thank you for meeting with us on Friday and for discussing many important issues. One item that I mentioned as being bothersome was the decision of the GPTP (Martin Brecher) to unilaterally block



implementation of the approved changes to the Adverse Reactions section of the Seroquel CDS which had been discussed and agreed to at the June 2000 SERM. Looking through the cascade of e-mails below, there are statements from Marketing stating their concerns about the deletion of the term "limited" as a qualifier of weight gain.

Since the e-mail of April 10th, it was decided to have Clinical (Martin Brecher) prepare a discussion document revisiting weight gain. Martin has done so citing a publication which he authored based upon long term clinical trials (open label extension trials) consisting of only a small number of patients (178). This will be presented at SERM on July 30, 2001. In Martin's discussion document there is currently no literature search to present published data on weight gain, much of which was done in short term clinical trials by AZ or individual case reports, and case series. After pointing this out to Martin last week, he then indicated that he was under the impression that I was preparing a second discussion document in parallel with his, which was not my original intent. I have since requested a literature search and if necessary will prepare an update to the existing discussion document to include relevant safety data. This entire issue has become a major point of contention between Clinical and Drug Safety and has consumed a lot of time and resources from Drug Safety.

What I don't understand is how the changes agreed to at SERM in June 2000 (which included Martin's participation and endorsement) could be held-up nearly 10 months later? Perhaps I am too close to the issue to understand if and where the process broke down. If you would, please share your perspective with me on this.

Thanks and best regards,
Wayne

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

From: Brecher, Martin
Sent: Tuesday, April 10, 2001 3:11 PM
To: Owen, Richard T; Oldham, Alex; O'Brien, Shawn P
Cc: Holdsworth, Debbie; Aked, Dominic M; Geller, Wayne; Dev, Vikram J
Subject: RE: Weight gain and CPI Justification document

Folks,

I spoke to Vikram who suggests that we revisit the issue at the next SERM. For now I'll write to Stefan Carlsson not to implement the removal of the word "limited". Vikram will speak to Wayne about preparing a discussion document incorporating the OLE b data for the next SERM.

Martin

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

From: Owen, Richard T
Sent: Tuesday, April 10, 2001 11:41 AM
To: Oldham, Alex; Brecher, Martin; O'Brien, Shawn P
Cc: Holdsworth, Debbie; Aked, Dominic M
Subject: FW: Weight gain and CPI Justification document

Dear Alex, Martin and Shawn
Please find below our comments on the proposed label amendment to remove the descriptor 'limited' from the weight gain statement.

We look forward to your comments on the best way forward.

Regards

Richard
(on behalf of Debbie and Dom)

RE: "As with other antipsychotics, SEROQUEL may also be associated with limited weight gain, predominantly during the early weeks of treatment".

We believe that the proposed label amendment of removing the word 'limited' from the above claim is potentially damaging to Seroquel. i.e.

While there were no reports of positive dechallenges and rechallenges, there is reasonable evidence to suggest that Seroquel therapy can produce significant weight gain in select individuals. Therefore, it is suggested that the qualifier "limited" be removed from the weight gain statement in the CDS

Areas that could be explored which would be more commercially orientated are:

- Can concomitant use of drugs that may cause weight gain be ruled out in each case? In many of the case reports concomitant therapy is not detailed, though we know polypharmacy is common
- Weight fluctuation is common. Can we rule out that the patients did not have a previous history of weight gain following treatment for their psychiatric illness. It could be that psychosis is associated with abnormal eating patterns
- The concluding statement suggests there are no 'Definitive' case reports to firmly establish the link..
- How does this data fit with the long term weight neutral data? If we are to amend the label with regards to weight, then this long-term data should also be reflected in the label. It could be argued that long-term weight data is at least or even more clinically meaningful than short term data. Also should the BMI data not carry more weight and be considered as part of the picture as a priority as it is internationally recognized as the most sensible way to assess weight changes?
- How frequent do we estimate the weight gain to be? Can we include this in the label?

We wonder whether weight gain should be kept under review at this stage.

Alternatively, if we are reviewing the label for weight, we should also reflect the weight neutral data from clinical trials alongside these case reports. In addition, do we need to reflect the limitations around the case reports:

E.G. incomplete information in many cases?

EG *there were no reports of positive dechallenges and rechallenges,*

The justification document does not mention the wording in the labels for competitors. Is this an oversight?

What is the best route to influence this discussion?

Kind regards

Richard, Debbie, and Dominic

From: Owen, Richard T
Sent: 10 April 2001 14:10
To: Holdsworth, Debbie; Ake, Dominic M
Subject: FW: Before April 25th - Review Seroquel Core Documents

Debbie/Dorn
For info, as discussed.

Richard.

From: Carlsson, Stefan SNC
Sent: 10 April 2001 13:53
To: Giddins, Russell E; Oldham, Alex; Owen, Richard T; Polinsky, Ronald; Brecher, Martin; Grant, Tom (WWRA); Dartee, Wim P; Jones, Martin AM (PHMS); O'Brien, Shawn P; Geller, Wayne; Rakic, Jasna; Livingston, Robert; Limp, Gerald L
Cc: Street, Paul R
Subject: Before April 25th - Review Seroquel Core Documents

Dear All,

Following SERM the current Seroquel tablet CDS and accompanying core documents need to be updated. According to the SOP for Global Product Information the amendments made to CDS will be reviewed by the RAD, members of the GPT, the Medical Affairs Manager, the site Head of Drug Safety, US Regulatory Affairs and other relevant persons. I hope I have not missed anybody but please feel free to obtain comments from other individuals you may find relevant but make sure all comments have been sent to me at the latest Wednesday April 25th, 2001.

Please find attached the draft CDS, draft CPIL, draft ACDS and the Justification Documents (JDs) that support the following changes to the CDS:

- the removal of the descriptor "limited" before "weight gain" in section 4.8,
- the addition of "hypersensitivity including angioedema" to section 4.8, and
- the removal of overdose statement in section 4.9.

Regarding the CPIL, the previous revision from last year of that particular document included the addition of the 300 mg tablet. That tablet strength were included in the draft version that went on review but had fallen out in the version signed-off and put on CR. This is a regrettable mistake to which I do not have an explanation. For this reason I have re-added the 300 mg tablet in this revision.

CDS.

CPIL

ACDS

<<File: Seroquel CDS Draft_W6.doc>>

<<File: Seroquel Draft CPIL_W6.doc>>

JD Overdose

JD Hypersensitivity

JD Weight gain

<<File: Author draft JD Seroquel Overdose W61.doc>>
<<File: Author draft JD Hypersensitivity W6.doc>>

<<File: Author draft JD WeightGain W6.doc>>

Kind regards
Stefan

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