Sok Central

Till: Wändel-Liminga Ulla; Melander Hans; Ahlström Lena
Ämne: VB: Eudralink - Prozac 20mg Capsules (PL 0006/0195) and Oral Liquid (PL 0006/0272) - FUM no. 2 (UK/H/0636/001,003) sexual maturation in children. Response to RFI no. 4

Bifogade filer: 011 Cover letter TADs Jr FUM RFI 4 Response 21May.doc; Eudralink.htm; Response 4 to MHRA_TADSJr and HCLU_17May2007_Apved.doc


011 Cover letter TADs Jr FUM R...


Eudralink.htm (6 KB)


Response 4 to MHRA_TADSJr and ..

1994-0112, Fontex®, 4 mg/ml, Oral lösning, UK/H/636/03, FUM 02; EMEA/H/A-6(12)/671, 2111:2006/63256

Svar på frågor -> IVB -> 0
/Eva P

-----Ursprungligt meddelande-----
Från: anderson_carly@lilly.com [mailto:anderson_carly@lilly.com]
Skickat: den 21 maj 2007 17:19
Till: Sok Central
Ämne: Eudralink - Prozac 20mg Capsules (PL 0006/0195) and Oral Liquid (PL 0006/0272) - FUM no. 2 (UK/H/0636/001,003) sexual maturation in children. Response to RFI no. 4

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Subject: Prozac 20mg Capsules (PL 0006/0195) and Oral Liquid (PL 0006/0272) - FUM no. 2 (UK/H/0636/001,003) sexual maturation in children. Response to RFI no. 4

From: anderson_carly@lilly.com

To: sok.central@mpa.se

Sent: Mon, 21 May 2007 16:18:52 +0100

Expiration: Tue, 5 Jun 2007 16:18:52 +0100

Reply

Dear Dr Riegl,

Please see the attached cover letter and response document.

Kind regards,

Carly Anderson
Eli Lilly and Company

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011 Cover letter TADs Jr FUM RFI 4 Response 21May.doc	MS Word Document	51kb
Response 4 to MHRA_TADSJr and HCLU_17May2007_Apved.doc	MS Word Document	63kb

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Phone: 44 (0) 1276 483162

Dr. Martina Riegl
Medicines and Healthcare products Regulatory Agency
Market Towers
1 Nine Elms Lane
Vauxhall
London SW8 5NQ

21 May 2007

Dear Dr. Riegl,

RESPONSE TO REQUEST FOR FURTHER INFORMATION

Prozac 20mg Capsules (PL 0006/0195) and Oral Liquid (PL 0006/0272) - FUM no. 2 (UK/H/0636/001,003), Post-licensing commitment to assess sexual maturation in children

With reference to your fourth request dated 2 May 2007 for further information regarding the above mentioned follow-up measure for fluoxetine and addendum HCLU, please find attached Lilly's response to this request.

If you require anything further, please do not hesitate to contact me.

Yours sincerely,

Dr Carly Anderson
Acting on behalf of Dr Diane Mackleston for Eli Lilly and Company fluoxetine MAHs.

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Email: anderson_carly@lilly.com

cc. Concerned Member State representatives

Fluoxetine Regulatory Response 4: Revised Response Assessment Report no. 2 Following CMS Comments on Post-licensing Commitment to Assess Sexual Maturation in Children

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Prozac®
(Fluoxetine hydrochloride)

UK/H/0636/001,003, FUM no. 2: 17 May 2007

The information contained in this document will undergo revisions, during the lifecycle of this plan, as new information about risks, exposures, and other important safety information about fluoxetine becomes available to the Global Product Safety division within Eli Lilly and Company.

Table of Contents

1. Background

As a post-licensing commitment, Lilly agreed to work with clinical investigators who are developing a prospective placebo-controlled trial to compare fluoxetine and cognitive behavioral therapy (CBT) in children with major depressive disorder to include the assessment of sexual maturation. Questions and comments regarding this proposed study were sent to Lilly on 2 November 2006 and responses were provided as requested on 16 November 2006.

On 19 December 2006, the MHRA submitted a second Request for Supplementary Information that assessed the response sent by Lilly on 16 November 2006, including additional comments from representatives from the Netherlands, France and Italy. The MHRA concluded that "Except for the question addressing the timing for consent to the sexual development study, none of the questions has been satisfactorily addressed. The MAH should satisfactorily address these questions." Lilly provided responses to these further questions and comments on 31 January 2007, based primarily on the 31 May 2006 Letter of Undertaking submitted by Lilly to the CHMP, who subsequently accepted and agreed with the conditions outlined in this letter prior to reaching a positive CHMP opinion on a paediatric indication for fluoxetine on 1 June 2006.

On 12 March 2007, the MHRA provided the third assessment which indicated that 5 issues had been resolved and 2 responses had been noted, leaving 5 issues for further comment. Lilly provided responses to these further questions and comments on 11 April 2007.

On 2 May 2007, the MHRA provided a fourth assessment which indicated that 3 issues/questions remain open for further comment. This response provides Lilly's commitments regarding these 3 outstanding issues for resolution.

2. Questions/Answers

Lilly provides responses to the request by the MHRA for further information regarding the following outstanding issues.

2.1. Serial Hormone Measurements

MHRA Comment:

The MAH have agreed to perform the hormone measurements. It would appear that the MHRA's request for serial measurements of LH and FSH has been misinterpreted as a request for single measurements. ***Issue resolved provided 6 monthly serial measurements of the gonadotrophins LH and FSH are provided.*** *Samples should be taken at 20 minute intervals for 120 minutes between 7.00 and 9.00 a.m.*

Response from Lilly:

Lilly agrees to conduct the 6-monthly serial measurements of the gonadotrophins LH and FSH provided the following:

- It is conducted under a third informed consent document (3 specific informed consent documents provided below, all previously proposed and agreed upon).
    - Informed Consent 1: TADS Jr. protocol (patients can participate in this only, if they choose)
    - Informed Consent 2: HCLU addendum (patients who are in the TADS Jr. protocol, can participate in this addendum also – without the serial blood draws, if they choose)
    - Informed Consent 3: HCLU addendum, serial blood draws (patients who are in the TADS Jr. protocol and HCLU addendum, can participate in all procedures, including the serial blood draws, if they choose)
- Enrollment in the main TADS Jr. protocol is in no way linked to enrollment in the HCLU addendum. To be clear, this would mean that the TADS Jr. protocol will conclude enrollment as specified, irrespective of the number of patients enrolled in any part of the addendum.

Lilly has serious concerns about the ability to enroll in this aspect of the trial and, in fact, believe very few, if any, parents will agree to have their child participate in this procedure.

2.2. Height, Weight, and BMI

MHRA Comment:

The MAH has agreed to collect height and weight data at each visit. The provision of BMI data is acceptable. ***Issue resolved provided data are analysed as follows:***

Height, weight and BMI should be expressed in standard deviation scores (z-scores) using normative data relevant to the study sites.

Change from baseline in height, weight and BMI z-scores should be calculated for the fluoxetine + CBT and placebo + CBT at 12 weeks and be compared using a parametric test. This will allow a direct assessment of the short term influence of fluoxetine on length and body composition/BMI growth.

Comparisons between treatment groups for the same parameters should also be undertaken fro each visit during the 104 weeks follow-up phase. Although it is acknowledged that height and weight may be influenced by other factors, such as treatments taken beyond the 12-week treatment period, the comparison between treatment groups is still a randomized comparison and can provide useful information.

Response from Lilly:

Lilly agrees to this type of statistical analysis and plans to use the US growth charts (CDC provided) as they are appropriate for all sites.

Reference: 2000 CDC Growth Charts: United States. National Center for Health Statistics. website: http://www.cdc.gov/growthcharts

2.3. Amended Draft Protocol

MHRA Comment:

An amended draft protocol should be submitted taking into consideration all amendments agreed in this procedure. The amended draft protocol should also address procedures for measuring height and weight and for specialized training and assessment of interrater reliability for Tanner rating.

Response from Lilly:

Lilly agrees to provide the amended draft addendum (Lilly Addendum HCLU) that accompanies the TADS Jr. study as soon as all outstanding items (only 2) are agreed upon. Lilly commits to sending this amended addendum within 2 weeks of agreement of the remaining items of discussion between the Lilly and the MHRA.

Additionally, Lilly has communicated with the TADS Jr. investigators and they have agreed to the following with respect to the interrater reliability for the Tanner stage ratings:

- Training will occur through the use of pictures that require 100% accuracy and that represent all 5 stages separately.
- A test of knowledge will be utilized for the adequately trained nurse practitioners, physicians, and/or physician assistants who will assess Tanner staging according to this addendum.

3. Conclusion

As previously stated, Lilly anticipates the fulfillment of the follow-up measures committed to in the Letter of Undertaking, dated 31 May 2006, and believes that these commitments bring us closer to resolving the outstanding issues and finalizing the protocol addendum.