Sok Central

Till: Wändel-Liminga Ulla; Melander Hans
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. 3

Bifogade filer: Eudralink.htm; 009 Cover letter TADs Jr FUM RFI 3 Response 12April.doc; Response to MHRA_TADS Jr and HCLU_11Apr2007_APPROVED.doc


Eudralink.htm (3 KB)


009 Cover letter TADs Jr FUM R...


Response to HRA_TADS Jr and H

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 FUM 02
IVB -> 0
/rs

-----Ursprungligt meddelande-----
Från: anderson_carly@lilly.com [mailto:anderson_carly@lilly.com]
Skickat: den 12 april 2007 13:21
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. 3

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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. 3
From:	anderson_carly@lilly.com
To:	sok.central@mpa.se
Sent:	Thu, 12 Apr 2007 12:20:48 +0100
Expiration:	Fri, 27 Apr 2007 12:20:48 +0100

1995-0254

Dear Dr Riegl,

Please see the attached cover letter and response document. Please note that the two publications referenced in our response will be provided shortly.

Kind regards,

Carly Anderson
Eli Lilly and Company

Filename	Type	Size
009 Cover letter TADs Jr FUM RFI 3 Response 12April.doc	MS Word Document	51kb
Response to MHRA_TADS Jr and HCLU_11Apr2007_APPROVED.doc	MS Word Document	78kb

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

12 April 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 third request for further information of 12 March 2007 regarding the fluoxetine TADS Jr. study and addendum, please find attached the responses to these questions and comments.

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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cc. Concerned Member State representatives

Fluoxetine Regulatory Response 3: Revised Response Assessment Report no. 2 Following CMS Comments on Post-licensing Commitment to Assess Sexual Maturation in Children

Prozac®
(Fluoxetine hydrochloride)

UK/H/0636/001,003, FUM no. 2: Approved: 11 April 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. This response provides Lilly's commitments regarding these 5 outstanding issues for resolution.

Lilly would also like to take this opportunity to keep the MHRA informed on the progress of the TADS Jr. study, to which the sexual maturation addendum is to be added. The TADS Jr. investigators informed Lilly on 26 March 2007 that they have revised their timeline and anticipate submitting their proposal to the NIMH for funding on 1 October 2007.

2. Questions/Answers

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

2.1. 104 Week Follow-Up

MHRA Comment:

The company's concern regarding attrition rates are noted.

A one-year follow-up period id considered inadequate given the age range of the trial population (8-12 years), the few assessments and the lack of sizable progression of puberty over 24 weeks. The MAH is reminded of their commitment letter to the CHMP of 31 Mary 2006 which stated that they are further investigating the possibility to have longer term evaluations at 52 and/or 104 weeks. A follow-up of five years would be desirable, a duration of 104 weeks after the 12-week double-blind treatment period is the absolute minimum that would be acceptable. ***Issue resolved provided the follow-up will be 104 weeks after the 12-week double-blind treatment period.***

Response from Lilly:

Lilly has discussed this addition for addendum B1Y-MC-HCLU with the investigators of the TADS Jr. protocol and they have agreed to the extended follow-up period of 104 weeks following the 12-week double-blind treatment period, provided Lilly funds this additional 2 years, which has been committed by Lilly. However, the TADS Jr. investigators did voice concern over the value of the data gathered during the 2-year open-label follow-up period. It is important to note that during this follow-up period, treatment will be the decision of the treating physician. This treatment may include fluoxetine, other antidepressants, or discontinuation of fluoxetine and all other antidepressants for time periods specified by the physician. Concomitant medication will be tracked, but the therapy during the follow-up period will be confounded with treatment response during the double-blind portion of the study and with any response made during the follow-up period itself.

2.2. Hormone Measurements

MHRA Comment:

The investigators point out that the blood draws would likely interfere with compliance in the trial, and children would likely refuse blood draws. To alleviate this concern, offering use of EMLA to reduce pain from needle insertion might be considered.

The MAH's comment that collecting blood in other studies was justified as there was a putative drug mechanism known to possibly effect the hormones is noted. Preclinical studies have raised a concern with respect to fluoxetine and its effect on sexual maturation; the measurement of hormones in children is considered mandatory

It is noted that no final study protocol was agreed as part of the post-licensing commitment.

Issue not resolved.

Response from Lilly:

While Lilly maintains the same reservations previously presented regarding the potential to add value of the hormone assessments, Lilly agrees to perform these assessments requested by the MHRA:

- blood draws at 9:00 a.m. (as recommended by the MHRA) at 6-monthly intervals to assess LH, FSH, testosterone (boys) and estradiol (girls)
- annual LHRH and prolactin assessments.

Given the ethical concerns previously stated and the likelihood that the time-specific nature of these blood draws might effect participation, Lilly proposes to utilize an additional informed consent document specifically for the collection and timing of blood samples which will allow patients to participate in other areas of the protocol and addendum even if parents have reservations about allowing their child to undergo blood tests. In an effort to possibly increase participation in the blood draws, Lilly will offer the possibility to use EMLA to reduce pain from needle insertion.

This proposal will provide the possibility and opportunity to collect the hormone data for assessment without deterring participation in the TADS Jr. protocol and/or sexual maturation addendum for those patients that refuse for whatever reason to participate in the blood draw.

2.3. Tanner staging

MHRA Comment:

The company has not supplied any evidence for the reliability and validity of Tanner staging through US qualified nurse practitioners.

The MAH's proposal to assess Tanner stages at baseline, week 12 and week 36 can be accepted. Further assessments should be carried out at 6-monthly intervals.

It would appear that the National Institute of Child Health and Human Development (NICHD) Study of Early Child Care and Youth Development allowed for assessment of

Tanner staging by nurse practitioners. However, central training was provided to ensure across-site consistency in Tanner staging and all clinicians had to be specifically certified for Tanner staging. (see http://secc.rti.org/display.cfm?t=m&i=Chapter_58_1).

If nurse practitioners are used in this trial, substantial specialized training will be required and interrater reliability should be tested.

Response from Lilly:

Lilly agrees to:

- adequately train the nurse practitioners, physicians, and/or physician assistants who will assess Tanner staging according to this addendum.
- ensure interrater reliability.
- conduct Tanner stage assessments at 6-montly intervals throughout the 104-week follow-up period in addition to those already defined during the 12-week double-blind treatment period.

During the 26 March 2007 meeting with the TADS Jr. investigators they discussed that physicians assistants will also be performing the Tanner staging. Lilly is not aware if the EU has a similar profession and therefore is providing the following links to better describe the role of physicians assistants:

- http://en.wikipedia.org/wiki/Physician_assistant
- http://www.aapa.org/spec/AAPAOM/OMPAInformation2.html
- http://www.paworld.net/whatpadoes.htm

2.4. Height and Weight

MHRA Comment:

The MAH does not plan to monitor height and weight, nor to correlate these parameters to sexual maturation. It is considered essential that height and weight are reported to evaluate how any delay in sexual maturation might impact upon the magnitude of the pubertal growth spurt and also the effects of fluoxetine on weight gain. The MAH's response is therefore not accepted, and the Protocol Addendum should be amended to include measurement of height and weight at each visit.

Response from Lilly:

Lilly agrees to collect height and weight data at each visit throughout the protocol and the 104-week follow-up period in order to assess the effect of treatment on the relationship of sexual maturity to growth.

However, Lilly remains concerned about the possibility to assess a correlation of height and weight with sexual maturation, specifically given the size of the study and the likely variability of the patients included in this study. Additionally, as would be the case for any treatment beyond the double-blind treatment period, it is unlikely that any meaningful conclusions can be made regarding this growth data and sexual maturation, given the possible effects of concomitant medications, diet, illness, and a multitude of possible confounding factors during the 104-week follow-up period.

Lilly has continued to evaluate possible correlations between height and/or weight and sexual maturation and proposes to calculate body mass index (BMI) as a means to correlate height/weight growth with sexual maturation. Burrows and colleagues (2004) and Bini and colleagues (2000) suggest that biological development is associated with BMI. While Lilly is agreeable to providing BMI measurements, reservations remain in the value of this information following the 104-week open-label follow-up period during which time any treatment may be administered.

2.5. Primary Analysis Variable

MHRA Comment:

The MAH states that their letter of undertaking provided the primary analysis variable. It is noted that no 'primary analysis parameter' was specified in the document the MAH refers to. The document does state that the MAH will propose to evaluate the percentage of patients that progress at least one Tanner stage in 12 weeks and after 24 weeks, with possibly also weeks 52 and/or 104. The MAH's response is therefore not accepted. ***Issue not resolved.***

Response from Lilly:

Lilly proposes the following text to be included in the protocol:

> "The primary outcome is considered a safety outcome. The primary analysis variable will be whether a patient has an increase in Tanner stage during the double-blind portion of the study. This same assessment will be conducted for the 104 weeks follow-up period to provide information requested by European regulators but will not be considered the primary analysis variable. The proportion of patients treated with fluoxetine in combination with CBT who have an increase in Tanner stage from baseline to either the end of the double-blind portion or the end of the 104 week

follow-up will be compared with the proportion of patients treated with placebo in combination with CBT using a Mantel-Haenszel test of difference in proportions stratified by site. For the analysis of the double-blind portion, only patients with both a baseline and a post-baseline double-blind observation will be included. For the 104-week follow-up, only patients with both a baseline and at least one long-term follow-up measurement will be included in the analysis comparing baseline to the last observed post-baseline Tanner stage."

There are several scientific reasons why Lilly does not consider the result at the end of 116 weeks (12 + 104) as primary. Firstly, the 104 weeks of post-therapy follow-up are open-label with no assigned therapy and as a result other therapy effects may confound and bias the assessment. Also, since the total time post-baseline is 116 weeks, a large proportion of children are likely to have a shift upward in Tanner stage. This would leave only a few, perhaps 5 to 15% who have not shifted, so that statistically, the magnitude of effect is similar as after 12 weeks but with the roles of "success" and "failure" reversed. Statistically there would be no difference in power except that at the end there will be fewer children available to observe lowering the ability to distinguish drug effect. Despite these reservations, Lilly agrees to provide the MHRA with an analysis of the 116-week data as requested. The statistical analysis plan will document further summaries of the Tanner stage data by visit.

2.6. TADS Safety Data

MHRA Comment:

In addition, please provide any data that you may have obtained or can obtain from the TADS investigators regarding the 18-week and 36-week efficacy and safety data from the TADS trial.

Response from Lilly:

Lilly discussed this request with the TADS investigators and were informed that a publication containing 18-week and 36-week data has been accepted for publication and is expected to be published in a few months. Lilly will provide this manuscript to the MHRA once published. Additionally, the full data set is tentatively scheduled to be made available in the public domain in May 2008.

3. Conclusion

As previously stated, Lilly is eager to fulfill the follow-up measures committed to in the Letter of Undertaking, dated 31 May 2006, and believes that this communication brings us closer to resolving the outstanding issues.

4. References

Burrows R, Diaz N, Muzzo S. 2004. Variations of body mass index (BMI) according to degree of pubertal development. Rev Med Chil 132:1363-1368.

Bini V, Celi F, Berioli M, Bacosi M, Stella P, Giglio P, Tosti L, Falorni A. 2000. Body mass index in children and adolescents according to age and pubertal stage. Eur J Clin Nutr 54:214-218.