RMS

Final Assessment Report

Post-licensing commitment to assess sexual maturation in children

CLINICAL

Prozac

(fluoxetine)

UK/H/0636/001,003

Applicant: Eli Lilly

Start of the procedure:	14 September 2009
Date of this report:	25 August 2010

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1 EXECUTIVE SUMMARY AND RECOMMENDATIONS

In 2006 the indication of Prozac™ was extended to include the treatment of children and adolescents aged 8 years and above suffering from moderate to severe major depressive episodes unresponsive to psychological therapy after 4-6 sessions.

As non-clinical data in rats had identified concerns regarding effects on sexual development, growth, and testicular toxicity the MAH undertook as a Postlicensing Commitment/Follow-up Measure (FUM) to conduct further preclinical studies and to clinically evaluate possible effects of fluoxetine treatment on sexual maturation in humans.

The MAH has conducted the required preclinical studies, confirming a delay in sexual maturation in rodents but apparently failing to elucidate a causal mechanism for this effect.

With respect to clinical evaluation, the MAH undertook to use registries in some EU Member States - if such registries could be identified - and to participate in a prospective placebo-controlled study of children with MDD which was to be performed by the NIMH (the TADS Jr study) and to explore possible effects of fluoxetine treatment on sexual maturation by protocol amendment.

The MAH could not identify any registries that might be used and brought forward various reasons for not setting up a prospective registry. Now the TADS Jr study will not be conducted because of lack of funding by the NIMH, and consequently the exploration of possible effects of fluoxetine treatment on sexual maturation as part of this study will not be feasible. The MAH therefore requests that the post-authorization commitment to clinically evaluate the effect of fluoxetine on sexual maturation to be considered fulfilled.

The RMS agrees that any clinical study to investigate the effects of fluoxetine on sexual maturation would be forbiddingly hard to conduct and difficult to interpret. The company's request that the FUM to clinically evaluate the effect of fluoxetine on sexual maturation be considered fulfilled is therefore accepted.

2 BACKGROUND

On 1 June 2006, following a European referral procedure article 6(12) of Commission Regulation (EC) No1084/2003, a positive opinion was adopted by the Committee for Medicinal Products for Human Use (CHMP) to extend the use of Prozac in combination with a concurrent psychological therapy to the treatment of children suffering from moderate to severe major depressive episodes unresponsive to psychological therapy after 4-6 sessions.

Non-clinical data in rats and mice submitted as part of the procedure had identified concern regarding effects on sexual development, growth, testicular toxicity and potential long-term neurobehavioural effects. Consequently, the MAH undertook as a follow-up Measure (FUM) to further investigate in juvenile rats the effects of fluoxetine on emotional behaviours, to explore the mechanism for and the reversibility of the testicular effects and to assess effects on the hypothalamic-pituitary-gonadal (HPG) axis during sexual maturation.

In addition, the MAH undertook to use registries in some EU Member States - if such registries could be identified - and to participate in a prospective placebo-controlled study which was to be performed by the NIMH (the TADS Jr study) to explore possible effects of fluoxetine treatment on sexual maturation.

A description of the pre-clinical effects and appropriate warnings regarding the need to monitor patients for events in relation to growth, pubertal development, hostility and suicide related behaviour were included in the SmPC. The information with respect to growth and pubertal development (section 4.4 the SmPC) is as follows: '*In a 19-week clinical trial, decreased height and weight gain was observed in children and adolescents treated with fluoxetine (see section 4.8). It has not been established whether there is an effect on achieving normal adult height. The possibility of a delay in puberty cannot be ruled out (see sections 5.3 and 4.8). Growth and pubertal development (height, weight, and TANNER staging) should therefore be monitored during and after treatment with fluoxetine. If either is slowed, referral to a paediatrician should be considered.'*

The MAH duly conducted an investigation to determine the existence of a European registry containing information on children and adolescents treated with fluoxetine that could allow for retrospective assessment of the effects on sexual maturation. No such registry could be identified. Consequently, the MAH was requested to investigate the possibility of setting up a prospective registry in the United Kingdom. The MAH considered the creation of a registry for branded Prozac was neither practical nor feasible as Prozac accounts for approximately 2% of fluoxetine prescriptions in the paediatric population, with the majority of prescriptions being for other branded/generic products,. A registry involving a joint effort between all fluoxetine MAHs working toward a common data collection protocol might be considered, but this strategy could be beset with logistical issues as children who are currently treated with generic formulations of fluoxetine are not required to undergo Tanner staging, as is required of those prescribed Prozac..

The MAH has now informed the UK that the TADS Jr study will not be conducted, and consequently the exploration of possible effects of fluoxetine treatment on sexual maturation as part of this study will not be feasible. The MAH therefore requests that the post-authorization commitment to clinically evaluate the effect of fluoxetine on sexual maturation to be considered fulfilled, stating that '*The approved SmPC accurately reflects the current knowledge regarding fluoxetine and sexual maturation and is appropriate and sufficient to allow physicians to safely prescribe fluoxetine in the paediatric population. The SmPC includes the direction that Tanner Staging should be conducted and the results monitored during and after treatment with fluoxetine, and recommends referral to a paediatrician if development appears slowed. Lilly believes this serves as an adequate risk minimization measure, and that the current SmPC recommendation would be unlikely to alter regardless of positive or negative results from a clinical data collection aimed at evaluating the effect of fluoxetine on sexual maturation.'*

3 PRECLINICAL DATA

Preclinical data that became available at various stages during the assessment of the variation to extend the use of Prozac for children are summarised in Table 1 below.

Table 1: Preclinical data available by June 2006

Species	Source	Main findings
Rat	MAH's juvenile toxicity study WIL-353039	Severe effects on body weight gain, sexual maturation in males and females, testes, skeletal muscles, sperm concentration at the dose of 30 mg/kg/day, some of these effects occurring at 10 mg/kg/day.
5HTT-/- transgenic mouse	Ansorge et al Science 2004, Vol 306, 879-881	Transient inhibition of 5-HTT during early development with fluoxetine, a commonly used serotonin selective reuptake inhibitor, produced abnormal emotional behaviours in adult mice.
Mice	Warden et al	5-HTT inhibition had significant detrimental effects on bone mineral accrual. 5-HTT null mutant mice had a consistent skeletal phenotype of reduced mass, altered architecture and inferior mechanical properties, while bone mineral accrual was impaired in growing mice treated with a SSRI.

Preclinical data that have become available as a result of the MAH's postlicensing commitment are summarised in Table 2. These have been assessed in the relevant MR procedures.

Table 2: Preclinical data available since June 2006

Species	Source	Main findings as summarised by the MAH in present submission
Rat	MAH's juvenile toxicity study 901143	Delay in sexual maturation in females, changes in FSH and LH levels No effects on FSH and LH in males, but significant change in Inhibin B. No information regarding absence or presence of delayed sexual maturation in male animals.
Rat	MAH's juvenile toxicity study 901144	Decreases in LH and Inhibin B, irreversible testis lesions
Rat	MAH's juvenile toxicity study F3	No effects of fluoxetine on 3 tests designed to measure emotional and sensory gating behaviour

Assessor's comment

Note that preclinical study reports have not been made available as part of this procedure.

4 AVAILABLE CLINICAL DATA

4.1 Data from the MAH's Postmarketing Safety (PMS) Database

A review of Lilly Safety System PMS database through 13 February 2009 was conducted using the High Level Term "Endocrine Abnormalities of Puberty". This includes the following Preferred Terms (PT): *delayed menarche, delayed puberty, early menarche, incomplete precocious puberty, precocious puberty, pseudoprecocious puberty,* and *true precocious puberty*.

The search identified 6 cases of "*delayed puberty*", 4 cases of "*precocious puberty*", and 1 case of "*early menarche*". Tables 3 and 4 summarise the information available for these reports. The CIOMs reports forms for these cases were submitted.

Table 3 Case Summaries for Children and Adolescents Experiencing Delayed Puberty during Fluoxetine Therapy

Case #	Age/Sex	Dose	Duration on medication	Concomitant Medications	Concomitant Disease	Pertinent information
US96061288A	16/M	20 mg	Not specified	Not specified	Not specified	Age 14, no growth spurt, lack of onset of puberty
US97011954A	14/M	20 mg	5 years	Not specified	Not specified	The patient had not experienced a growth spurt, no facial hair growth, and was not interested in girls.
US_981214960	16/M	20 mg	2 years	Not specified	Depression	Age 16, no signs of puberty
US_991029746	14/M	60 mg	3 years	Not specified	Obsessive- Compulsive Disorder	Age 14 had not started puberty
US_010769080	11/F	13 mg	21 months	Methylphenidate	Dysthymia; anxiety; ADHD	Reduced growth from 90th to 50th percentile, weight, decreased appetite.
US_021088798	12/M	20 mg	12 months	Methylphenidate , fluvoxamine	ADHD	Tanner 2 pubertal signs appeared at age 14 years; Tanner 4 at age 15 years.

Table 4: Case Summaries for Children and Adolescents Experiencing Precocious Puberty or Early Menarche during Fluoxetine Therapy.

Case #	Age/Sex	Dose	Duration on medication	Concomitant Medications	Concomitant Disease States	Pertinent information
US_990522456	9/M	Not specified	180 days	Valproate Sodium; Sorbitol	Landau-Kleffner syndrome; Seizures; Encephalopathy; immune deficiency; Autism; Overgrowth syndrome	Patient's weight 77.3 kg, height 139.7 cm. Some time after starting fluoxetine began developing pubic hair.
US96072353A	5/F	4 mg	3 mo	Not specified	unremarkable	Patient on fluoxetine for 3 months, started growing pubic hair and her labia have started developing prematurely.
US94120190A	10/M	10 mg 2/d	545 days	Methylphenidate	Adopted child, so unaware of related family history	Precocious puberty diagnosed by endocrinologist. Bone X-rays showed 2 to 2-1/2years ahead in development.
US94090064A	8/F	20 mg	Months or a year	Dexamfetamine sulfate; Clonazepam	Not specified	Onset of puberty in an 8 yr old patient.
US96032536A	8/F	10 mg	Not specified	Not specified	Not specified	"Started on fluoxetine and got her period ".

Assessor's comment

The signal regarding sexual development was identified from preclinical studies. None of the paediatric trials performed by the MAH formally assessed effects on puberty or relevant endocrine parameters, nor did the TADS trial or the published fluoxetine relapse prevention trial (Emslie et al Am J Psychiatry. 2008 Apr;165(4):459-67). In any case, the duration of these trials would have been of inadequate duration to demonstrate any effect of fluoxetine on sexual development.

The MAH states that '*comparing these 11 cases with an estimated worldwide cumulative fluoxetine exposure of 2.758 million children and adolescents (< 18 years of age) as of Q4 2007 indicates that such events have a reporting rate of 0.0004% which qualifies as very rarely reported*'. This calculation of incidence is not appropriate, as the case reports are derived from spontaneous reporting and as such underreporting cannot be excluded.

Note that the search strategy did not include menstrual or sexual disorders. There are conflicting data from previous searches submitted by the company probably because different search terms were used:

(1) A previous database search performed by the MAH and covering a 5-year time period (March 2000 - March 2005), had identified 4 cases with penis disorders (2 priapism, 1 erectile dysfunction and one hypospadia in an infant), 13 cases of menstrual irregularity, 2 cases of delayed puberty (both exposed concomitantly to methylphenidate) and 7 cases of other various disorders. (Source: Rapporteur's Assessment Report of Referral Procedure[1] dated 31 October 2005)

(2) An additional search of the Eli Lilly and Company post-marketing adverse event database (Clintrace) was previously conducted for 41 different events indicating delayed sexual maturation or sexual dysfunction occurring in patients 18 years of age or younger. During the 21-year time period covered by the Clintrace search, a total of 26 such events were reported for this age group. (Source: Co Rapporteur's Assessment Report of Referral Procedure dated 31.10.05)

In the latest database search similar numbers of events have been identified for both delayed and precocious puberty. A causal relationship of any of these events to fluoxetine cannot be established based on the information available from the case reports. The direction of any effect of fluoxetine on sexual development would likely be in one direction only (i.e. either delay or early onset of puberty), with preclinical data pointing to the direction of delayed puberty. The assessment of the preclinical studies concluded that overall the neurohormonal rat study did not provide evidence of an association between delayed sexual maturation and inhibition of GnRH release, although confirmation was requested from the MAH.

A search of the MHRA database for spontaneous adverse event reports has not identified any cases of endocrine abnormalities of puberty.

Recognition and effective treatment of psychiatric disorders such as depression are essential in preventing child and adolescent suicides. Given that suicide is a leading cause of death among adolescents representing a significant public health problem, and depression is a strong predictor of suicide attempts and completion, even irrefutable evidence of delayed sexual maturation in humans would likely not render the risk/benefit ratio for the general population of 'children and adolescents with moderate to severe major depressive episode unresponsive to psychological therapy after 4-6 sessions' negative. The RMS agrees with the MAH's point of view that additional clinical data would be unlikely to alter the product information.

[1] Referral under article 6(12) of Commission Regulation (EC) No1084/2003, EMEA/H/A-6(12)/671

4.2 Data from literature

The MAH performed a literature search which did not reveal any published human studies relating to antidepressants and effect on puberty or sexual maturation. One publication was identified discussing four children with decreased growth during therapy with SSRIs (Weintrob et al, Arch Pediatric and Adolesc Medicine 2002, 156(7),696-701)

Assessor's comment
The assessor's literature search did not identify any additional studies or case reports relating to any impact that antidepressants may have on puberty or sexual maturation, nor any publications relating to any impact depression itself may have on puberty/sexual development.

5 OPTIONS FOR OBTAINING FURTHER CLINICAL DATA

The MAH has explored and judged as unfeasible various ways of obtaining additional clinical data with respect to sexual development. Table 5 summarises the options explored and the reasons for rejecting them.

Table 5: Options explored for obtaining additional data for sexual development

Option	Reason for rejection
Clinical trial specifically designed to investigate sexual development	Recruitment challenges arising out of public discussion regarding the use of SSRIs in the child and adolescent population
Data collection as part of NIMH-sponsored TADS Jr trial	TADS Jr trial will not be conducted as now not sponsored by NIMH
Use of existing registries to obtain retrospective data	Existing registries do not include relevant data; problems with privacy restrictions in some countries
Set up a UK registry to obtain prospective data	Most prescriptions for fluoxetine are for generic products which do not necessarily contain paediatric indication and relevant warnings.
GPRD study	Tanner stages not recorded in GPRD kan ngt om tillväxt får därifrån ?
European College of Neuropsychopharamcology (ECNP) study	Study has been amended to investigate risperidone only

Formaterat: Svenska (Sverige)

A discussion of the reasons is contained in the MAH's FUM response document. The reasons for rejecting the conduct of a clinical trial were extensively discussed as part of the referral procedure and are not repeated here.

The MAH now requests that the post-authorization commitment to clinically evaluate the effect of fluoxetine on sexual maturation to be considered fulfilled - without conducting any clinical evaluation at all.

6 RECOMMENDATIONS

The RMS agrees that any clinical study to investigate the effects of fluoxetine on sexual maturation would be forbiddingly hard to conduct and difficult to interpret. The company's request that the FUM to clinically evaluate the effect of fluoxetine on sexual maturation be considered fulfilled is therefore accepted.