Fluoxetine Hydrochloride

Response to Toxicology Questions from the Medicines and Healthcare Products Regulatory Authority and Agence Française de Sécurité Sanitaire des Produits de Santé, as Joint Reference Member States for Fluoxetine Hydrochloride

[redacted]

Eli Lilly and Company
Lilly Corporate Center
Indianapolis, Indiana

22 January 2009

Table of Contents

Fluoxetine Hydrochloride

Response to Toxicology Questions from the Medicines and Healthcare Products Regulatory Authority and Agence Française de Sécurité Sanitaire des Produits de Santé, as Joint Reference Member States for Fluoxetine Hydrochloride

The regulatory officials from the Medicines and Healthcare Products Regulatory Authority (MHRA) and Agence Française de Sécurité Sanitaire des Produits de Santé (Afssaps) have raised the following issues related to Fluoxetine hydrocholoride. Our responses to the recommendations and questions follow.

Section 6. RECOMMENDATIONS

Further Research

Recommendation 1

In order to address potential specific effect of fluoxetine to the rat, mechanistic studies in the juvenile rat could be performed. For example, carrying out a study in the juvenile rat expose to norfluoxetine could provide data indicating whether toxicity is mediated by fluoxetine or norfluoxetine. As levels of norfluoxetine are higher in the rat than in the human, slightly higher safety margins could be achieved if norfluoxetine is demonstrated to be the active component of the testicular toxicity (i.e. safety margin of 3.6 to 16.3 based on norfluoxetine levels at steady state for preadolescents as previously reported, compared to 0.8-8.8 based on fluoxetine levels) (see annex 1). Performing a juvenile toxicity study in a second species could also allow addressing species specificity.

Response to Recommendation 1

Testicular lesions in juvenile rats given fluoxetine is a high dose effect and is limited to doses that exceeded the MTD. Additionally, since adult male rats given S-norfluoxetine have also developed testicular lesions (Vodicnik et al. 1990), Eli Lilly and Company does not believe that any further study of fluoxetine compared to S-norfluoxetine in juvenile animals would fundamentally alter the benefit/risk analysis for clinical use.

Concerning performing a juvenile testicular toxicity study in a second species, mammalian spermatogenesis is qualitatively similar across species (Sharpe 1994). Most morphologic features of spermatogenesis are present in the rat, and the rat is the most widely used animal model for reproductive toxicity (Russell et al. 1990). Moreover, no one laboratory animal species is most predictive of human risk (Amann 1982), and it is not uncommon to have findings in one laboratory animal species that do not translate to other laboratory animal species or man. Eli Lilly and Company also remains convinced that performance of a juvenile nonrodent study (eg, in dogs) would be of limited value for elucidating these effects, due to technical (data interpretability) issues, including:

- Sexual maturation: evaluation is confounded by high variability in time to maturation in the dog and high inter-animal variability (Feldman and Nelson 1987; James and Heywood 1979; Kawakamiu et al. 1981).
- Testicular toxicity: evaluation is confounded by the high incidence of background lesions in the testes of the dog (Reams et al. 2000; Rehm 2000).

Together these points suggest that further testing in a second juvenile species or examination of exposure to norfluoextine alone, are unlikely to provide additional perspective on human risk.

Recommendation 2

Taken into account that SSRI, also sharing a common pharmacological activity, possess some specificity, such as a long plasmatic half life for fluoxetine, potential toxicological differences between fluoxetine compared to other SSRI should be address. Data derived from available juvenile toxicity studies performed in the rat with other SSRI should be reviewed.

Response to Recommendation 2

Eli Lilly and Company is not aware of available juvenile toxicology data for other SSRIs, but would welcome an opportunity to participate in a broader industry discussion of juvenile toxicity associated with SSRI pharmacology.

SmPC AMENDMENTS

Recommendation

Once data confirming an absence of a treatment related effect on FSH and LH levels has been provided, the MAH will be requested to submit a type II variation to update Section 5.3 of the Prozac SmPCs with the study findings in order to inform prescribers that the testicular pathology and delayed sexual maturation are not SSRI class effects mediated through an action on the hypothalamus.

Response to Recommendation

Eli Lilly and Company has completed three pharmaco-toxicological studies in juvenile rats following the approval of the extension of the indication of fluoxetine to include the treatment of a moderate to severe major depressive episode, if depression is unresponsive to psychological therapy after 4–6 sessions, in children and adolescents aged 8 years and above (EMEA/H/A-6(12)/671). In agreement with the EMEA the studies were:

- A Neurohormonal Study of LY110140 Administered by Oral Gavage in Young Rats (Study 901143)
- A Testicular Pathogenesis Characterization of LY110140 Administered by Oral Gavage in young Rats Followed by a Recovery Period (Study 901144)
- An Emotional Behavious Study in Sprague-Dawley CD Rats Given Fluoxetine or Paroxetine Daily by Gavage from Postnatal Day (PND) 33 to 62 (Study F3)

A follow-up measure (FUM) was also established:

> "If the RMS considers that the results of the preclinical studies warrant label changes or further study, we agree to discussions with the RMS to assess what further measure would be valid, useful and achievable."

The final study reports for 901143 and 901144 were submitted on 16 November 2007, and the F3 final study report was submitted on 29 August 2008. The recommendation to update Section 5.3 of the SmPC has resulted from the assessment of Studies 901143 and 901144 only, with Study F3 still under assessment. In accordance with the FUM, Eli Lilly and Company proposes that discussions relating to any potential update of Section 5.3 are delayed until all three studies have been assessed.

However, regarding the recommendation of the current assessment report, Eli Lilly and Company does not believe that the results of Studies 901143 and 901144 warrant any changes to the information already in the SmPC. The information provided by Study 901143 (juvenile neurohormonal study) and Study 901144 (juvenile testicular toxicity study) confirm the presence of the previously identified testicular lesions and established that there was no effect of fluoxetine on the hypothalamic-pituitary-gonadal (HPG) axis in maturing rats. Thus, these data do not effect the benefit risk assessment.

Section 7. LIST OF QUESTIONS TO BE ADDRESSED BY THE MAH

Female Reproductive Toxicity

Question 1

With regard to the statistically significant increase in Inhibin A levels at 10 mg/kg at Day 50 pp, the MAH stated that a closer examination of individual hormone data showed evidence that the difference in Inhibin A between the control and 10 mg/kg dose group, was most likely related to the distribution of animals to the different phases of the estrous cycle with more rats in the 10 mg/kg dose group in the follicular phase than controls and not related to treatment with fluoxetine. However the MAH must discuss the possibility that fluoxetine might have been responsible for the distribution of the animals to the different phases of the estrous cycle through potential effects on the cycle

Response to Question 1

Data from the rat juvenile toxicity study (Beck 2004) demonstrated that there were no effects of exposure to the high dose of fluoxetine on estrous cycle length. Estrous cycle data was not collected in the juvenile neurohormonal study (Adamo-Trigiani 2007b) as the design of this study was focused on examining the HPG axis. However, estrous cyclicity was established in the juvenile neurohormonal study by the presence of circulating hormone levels consistent with the follicular and luteal phases of the estrous cycle.

Question 2

The MAH must provide a profile of FSH and LH release over the duration of treatment for each dose level to determine whether there was a dose related trend.

Response to Question 2

Data was provided in the juvenile neurohormonal study (Adamo-Trigiani 2007b) showing FSH and LH levels on PND28, 30, 33, 35, 44, and 50. This covered the pre-pubescent (PND28) and peri- / post- pubescent period (PND30, 35, 44, and 50). Differences in circulating hormone levels across treatment groups appeared related to the state of sexual maturation rather than the dose level. Hormonal profiles in rats that were not sexually mature, regardless of treatment group, were similar to levels seen in sexually immature controls. Once rats showed signs of vaginal opening, the hormone levels detected were consistent with estrous cyclicity and were similar between the control and treated groups. Thus, while the timing of the attainment of vaginal opening appeared to be dose-related, the data from the juvenile neuroendocrine study (Adamo-Trigiani 2007b) demonstrated that the feedback loop control of LH and FSH was intact.

Basal gonadotropin levels are a reflection of the pulse pattern of hormone secretion. All blood samples were taken in the morning during a period of basal secretion of the gonadotropins. Mean basal hormone levels are made up of the hormone levels taken at one point in time from 10 rats, which, by random distribution, may have been at the ascending, peak, or descending part of the hormone secretion pulse, or in the interpulse interval during which there is little or no secretion of gonadotropins. Since basal hormone secretion did not differ between the treatment groups and is a reflection of the pulse pattern of LH and FSH secretion (Adamo-Trigiani 2007b), there is no data to support an effect of treatment on gonadotropin secretion dynamics.

Question 3

The MAH must provide a table correlating food consumption, bodyweight data and onset of sexual maturation on an individual animal basis for the male and female rats.

Response to Question 3

The juvenile neurohormonal study was a focused special study designed to examine the functioning of the HPG axis over the period of sexual maturation in male and female rats (Adamo-Trigiani 2007b). External signs of sexual maturation, vaginal opening and preputial separation, were evaluated only at termination. Thus, the exact day that vaginal opening or preputial separation occurred was not determined in this study nor could it be predicted in animals not sexually mature at termination. Food consumption was not evaluated in this endocrine-focused study. Thus, there is insufficient data from the juvenile neurohormonal study to generate the requested table.

Male Reproductive Toxicity

Question 4

The MAH must investigate the possibility of a mechanism of toxicity occurring locally in the male reproductive tract. The fact that statistically significant changes in Inhibin B have occurred in two independent studies is evidence that it might be an important marker of toxicity and its role (if any) in the pathogenesis of the testicular findings should be further investigated.

Response to Question 4

While the mechanism of testicular toxicity, which occurred at a nontolerated dose, is unknown, the endocrine data (Adamo-Trigiani 2007b) does not support an involvement of the HPG axis or the use of Inhibin as a biomarker of toxicity. Slight changes in circulating levels of Inhibin B were not consistent amongst studies (Adamo-Trigiani 2007a; Adamo-Trigiani 2007b). A slight increase in Inhibin B levels were noted on PND61 in male rats given daily doses of 30 mg/kg of fluoxetine (Adamo-Trigiani 2007b). This, slight increase in Inhibin B was not accompanied by a change in FSH levels. Thus, this change was of no physiological significance with regards to the functioning of the endocrine system. In the male testicular toxicity study (Adamo-Trigiani 2007a), Inhibin B levels during the treatment phase were examined on PND55, 70, and 91. There was no alteration in Inhibin B levels in males treated with 30 mg /kg of fluoxetine on PND55 or 70, a time frame that brackets the PND61 period in the juvenile neuroendocrine study (Adamo-Trigiani 2007b). While a slight decrease in circulating Inhibin B levels was seen at PND91 the male testicular toxicity study (Adamo-Trigiani 2007a), again this occurred with no accompanying change in FSH levels. Thus, this slight lowering of Inhibin B levels had no physiological impact on the functioning of the HPG axis. Moreover, by the end of the recovery period when testicular lesions were still present, Inhibin B levels in rats previously exposed to 30 mg/kg of fluoxetine were not different than levels seen in the vehicle control group (Adamo-Trigiani 2007a). These data do not support the mechanistic involvement of Inhibin B level or its use as a potential marker of the juvenile testicular toxicity of fluoxetine.

Question 5

The applicant should discuss the potential species specificity of the effects observed in the juvenile rat, in relation to the effects observed on Inhibin B and to exposure to fluoxetine versus Norfluoxetine. The relevance of performing a study in a second species should be addressed.

Response to Question 5

Testicular lesions in juvenile rats given fluoxetine were limited to doses that exceeded the MTD, and based on the results of careful histopathologic and neurohormonal evaluations (Adamo-Trigiani 2007a), were not linked to disruption of the HPG axis.

Since testicular lesions were not reported in toxicity studies using mature rats, no Inhibin B, or other endocrine data were collected in these standard toxicology studies. However, published results in adult Long-Evans rats exposed to fluoxetine showed no alteration from controls in testosterone or other measures of reproductive physiology (Taylor et al. 1996), lending further support that alteration of the HPG axis is an unlikely mechanism of toxicity in adult or juvenile rats.

Histologic findings in the juvenile studies were consistent with both germ cell (exfoliation, disarray, multinucleated giant cell formation, single cell necrosis, and full or partial loss of germinal epithelium in affected tubules) and Sertoli cell injury (vacuolation) (Beck 2004; Adamo-Trigiani 2007a). Although decreases in Inhibin B may reflect Sertoli cell dysfunction or injury, changes in Inhibin B in this study were within physiologic range, did not correlate on an individual animal basis with histologic findings in the juvenile toxicity study (Adamo-Trigiani 2007a), and were insufficient to exert a feedback effect on the HPG axis. Therefore, these alterations were not considered physiologically or toxicologically important. In addition, the data do not support the use of Inhibin B as a biomarker of injury, since gross and microscopic testicular findings were present in the absence of physiologically significant changes in Inhibin B. Overall, the endocrine data did not support alteration of the HPG axis as a mechanism for testicular toxicity.

Please refer to the response to the Response to Recommendation 1 for a discussion of further studies examining fluoxetine versus norfluoxetine or a second species.

Question 6

The applicant should discuss the potential specificity of the effects observed in the juvenile rat with fluoxetine compared to other SSRI, based on available data

Response to Question 6

Lilly would welcome an opportunity to participate in a broader industry discussion of juvenile toxicity associated with SSRI pharmacology.

References

Adamo-Trigiani M. 2007a. A testicular pathogenesis characterization of LY110140 adminstered by oral gavage in young rats followed by a recovery period. Document ID 901144. Eli Lilly and Company. Performing laboratory: Charles River Laboratories.

Adamo-Trigiani M. 2007b. A neurohormonal study of LY110140 administered by oral gavage in young rats. Document ID 901143. Eli Lilly and Company. Performing laboratory: Charles River Laboratories.

Amann RP. 1982. Use of animal models for detecting specific alterations in reproduction. Fund App Toxicol 2:13-26.

Beck MJ. 2004. A study in young CD(IGS) rats administered fluoxetine hydrochloride (LY110140) orally by gavage to evaluate general, reproductive and behavioral toxicity, study. Document ID WIL-353039. Eli Lilly and Company. Peforming laboratory: WIL Research Laboratories.

Feldman EC, Nelson RW. 1987. Canine female reproduction. In: Feldman EC, Nelson RW, editors. Canine and feline endocrinology and reproduction. Philadelphia, PA: WB Saunders Co. p 399-480.

James RW, Heywood R. 1979. Age-related variations in the testes and prostate of beagle dogs. Toxicology 12(3):273-279.

Kawakami E., Tsutsui T, Ogasa A. 1991. Histological observations of the reproductive organs of the male dog from birth to sexual maturity. J Vet Med Sci 53(2):241-248.

Reams RY, Hyten MJ, Swisher DK, Fisher LF. 2000. Evaluation of the mature canine male reproductive tract for toxicology studies. Phoenix (AZ): 19th Annual Symposium of the Society of Toxicologic Pathologists.

Rehm S. 2000. Spontaneous testicular lesions in purpose-bred beagle dogs. Laboratory Animal and Molecular Pathology. Toxicologic Pathology, vol 28, no.6, 782-787.

Russell LD, Ettlin RA, Sinha Hikim AP, Clegg ED. 1990. Mammalian spermatogenesis. In: Histological and histopathological evaluation of the testis. Clearwater (FL): Cache River Press. p 1-40.

SharpeRM. 1994. Regulation of spermatogenesis. In: Knobil E, Neill JD, editors. The physiology of reproduction, 2nd ed. New York (NY): Raven Press, Ltd. p 1363-1434.

Taylor G, Bardgett M, Csernansky J, Early T, Haller J, Scherrer J, Womack S. 1996. Male reproductive systems under chronic Fluoxetine or trimipramine treatment. Physiology and Behavior 59(3):470-485

Vodicnik MJ, Gries CL, Snyder SM .1990. A subchronic toxicity study of LY215229 maleate hemihydrate given by gavage to female fischer 344 rats for 1 month with interim and 1-month reversibility components. Toxicology Report 16. Eli Lilly and Company