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PROZAC (fluoxetine) – Paediatric indication

JOINT ASSESSMENT REPORT

Evaluation of company's response to list of outstanding Questions

Updated following comments from DK, FR, IE, SE and UK

Rapporteur:	Dr. Barbara van Zwieten – Boot
Co-Rapporteur:	Dr. Tomas Salmonson
Arbitration Procedure restart date:	15 September 2005
Date of Revised Consolidated Draft List of Outstanding issues	14 November 2005
Date of Joint assessment report	6 February 2006
Deadline for CHMP members' comments	13 February 2006

ADMINISTRATIVE INFORMATION

Invented name of the medicinal product:	Prozac
INN (or common name) of the active substance(s):	Fluoxetine
MAH in the RMS:	Lilly France S.A.S
Indication(s)	MDD, OCD, Bulimia Nervosa
Pharmaco-therapeutic group (ATC Code):	NO6A BO3 Selective Inhibitor of Serotonin Reuptake (SSRI)
Pharmaceutical form(s) and strength(s):	Capsules, 20 mg fluoxetine Oral solution, 20 mg fluoxetine per 5 ml
Rapporteur: **Rapporteur contact person:**	Name: Tel: Fax: Email: Name: Tel: Fax: Email:
Co-Rapporteur's contact person:	Name: **Ulla Liminga, PhD** Tel: + 46 18 17 47 47 Fax: Email: ulla.liminga@mpa.se
Names of the Rapporteur's assessors:	Clinical: Name: Tel: Fax: Email: Preclinical Name: Tel: Fax: Email:

Names of the Co-Rapporteur's assessors:	Non-clinical: Name: **Ulla Liminga** Clinical: Name(s): **Tomas Salmonson (PK), PhD** **Hans Melander (Efficacy)** **Pär Hallberg (Safety), MD, PhD**
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I. RECOMMENDATIONS

Prozac (fluoxetine) is registered for the treatment of major depression and various other indications in adults. The company has submitted a request to extend the indication to the treatment of major depression in children and adolescents aged 8 to 17. As no agreement about this request could be reached, a referral procedure was initiated with the NL and SE as rapporteur and co-rapporteurs, respectively. The second round of this procedure is currently in process.

Evidence for efficacy is based on three short-term clinical trials (HCJE and X065 were company sponsored trials and the TADS was an NIMH sponsored trial). Children and adolescents were included in these trials after they had had gone through an extensive assessment period that lasted 3 weeks and included three diagnostic interviews with three different psychiatrists, to be followed by a 1-2 weeks single-blind placebo lead-in period. Only those patients who remained sufficiently depressed throughout this period (i.e. continued to meet inclusion criteria) were included in the trials and randomised to receive double blind treatment with placebo or fluoxetine. The proportion of patients who were thus selected varied between 15% and 50% (depending on the trial) of the initially recruited patients, thus rendering the included patients a highly selected group that is not likely to be representative of the total patient population of depressed children and adolescents. Results of these trials showed moderate efficacy in the patient population that was included.
Long-term efficacy was explored in a small (n=40) randomised withdrawal trial with inconclusive results – depending on how the missing values were defined the results were or were not significant.

With respect to safety, the main problem identified was that of suicidality. This problem has been addressed, as for other SSRIs, by placing a warning in the SPC. In addition, the results of the trials indicated that fluoxetine treated patients had slower growth in terms of height and weight compared to placebo treated patients (although the differences decreased with continued treatment). Additional safety concerns are derived from non-clinical studies showing impaired growth including bone development, impaired sexual development as well as behavioural effects.
Long-term safety effects have not been investigated.

With the current response, the MAH submitted a new report (Nov-05): *Clinical Study Report from Kaiser Permanente on Study B1Y-MC-HCLS - The Association of Fluoxetine with Growth in Children and Adolescents at Kaiser Permanente in Northern California.* This is a retrospective case-control study, which has limitations, some of them inherent to the design of the study. Certain clarifications concerning the results of this study are requested. Nonetheless, the results of this study provide some reassurance that the impact of fluoxetine on growth may be not very significant. The evidence derived from the study suggests that cases are more ill than controls, which is likely to cause an overestimation of a negative effect of fluoxetine on growth, if one exists. Nevertheless, the study focuses only on growth and hence does not address the other identified safety concerns (bone development, sexual maturation, cognitive functions and behaviour, suicidality).

The responses of the company at this time (for a detailed assessment of these responses see section II of this report) indicates that the company is not intending to carry out any more studies to address the unresolved safety concerns. Specifically, the company has indicated to be unwilling to undertake additional non-clinical studies in a non-rodent juvenile model, or to address emotional behaviour or mechanisms behind testicular toxicity. Furthermore, the MAH declares that they have no intention to undertake the previously discussed clinical long-term study. The company is currently discussing with the FDA the possibility of not carrying out study (HCLT) which was designed, as a post marketing commitment to the FDA, to study efficacy and safety in a clinical population.
The lack of willingness on the part of the company to carry out additional studies that would elucidate safety concerns is disappointing, as the MAH has a clear responsibility for evaluation of safety in this population. Thus, the request for animal toxicity studies remains. Furthermore, the Applicant should re-discuss the possibility of a clinical study as proposed (study HCLT) and discuss other ways of studying the clinical long-term safety.

There are a number of issues to take into account in the benefit/risk assessment. The medical need for anti-depressant treatment of children and adolescents needs to be acknowledged as well as the fact that SSRIs, including fluoxetine, are used 'off label' in this population.
This reality underscored the need for gaining additional safety information via (pre)clinical studies and post-marketing surveillance. Both rapporteur and co-rapporteur recognise the safety concerns and agree that additional evidence should be collected in order to address these concerns. Regarding the non-clinical studies that would be required, the views differs. The rapporteur considers that a well-designed study to assess effects of fluoxetine on emotional development would be helpful to evaluate the influence and reversibility of these effects. This view is supported by IE, FR, and to some extent by DK (some studies are viewed as necessary and others not). The co-rapporteurs' view is that there are already signals from the clinic, and thus a negative result from a non-clinical study (i.e. pointing to no risks) would not override these clinical concerns. Although a positive result would confirm the identified concerns, it would not help risk assessment, especially since it has to be acknowledged that the interpretation of any animal model to address emotional behaviour and assess relevance for a depressed child is very difficult. This view is supported by ES **The issue will have to be discussed further in the CPMP.**

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In addition to elucidating safety issues, there is agreement about the need to provide, in the product information, evidence with respect to efficacy and safety concerning treatment of children and adolescents. The specific form in which this information should be conveyed still needs to be discussed. The form in which the information is provided depends to a large extent on the view regarding efficacy, an area where the rapporteur and co-rapporteur differ. The rapporteur considers that short-term efficacy was demonstrated only for a highly selected group of patients. Therefore, giving the indication would imply that in practice many patients will be unnecessarily treated. Hence, patients who may be responsive to psychosocial interventions or may recover spontaneously within a short time period, may be unnecessarily exposed to fluoxetine treatment. This would be especially worrisome in view of the safety concerns. A restricted indication is not possible either, as the basis for the restriction are, as of yet, unknown.

The co-rapporteurs' view is that the selection procedure used in the studies was adequate in that it excluded patients who did not consistently meet diagnostic criteria for depression. However, the problem is that in actual treatment settings such a rigorous selection is not likely to occur and hence many patients who are similar to those who were excluded from the studies will end up being treated in these settings, without evidence to support such treatment (view of the rapporteur). In addition to the issue of short-term efficacy, the broader issue of the balance between efficacy and safety in children and adolescents include additional issues, namely the weak evidence for long-term efficacy and the concerns about safety. If a general indication for the treatment of episodes of major depression in children would be accepted; then the problem of patient selection as mentioned above could be solved by describing the data in section 5.1. This view is supported by ES

Alternatively, in view of the potential risks, a more restricted indication could be discussed. The MAH suggest to limit the indication to chronic moderate to severe depressive episodes. This is based on the selection procedure. However the company did not provide evidence to support the severity. For adults the indication severe depression is rarely approved and only when specifically studied. Moreover, it does not address the problem identified by the rapporteur regarding the highly selected population. Other ways of limiting the use would be to limit the indication to include only adolescents, since the identified safety concerns are most worrisome for the younger part of the population under discussion, i.e. children compared with adolescents having reached puberty. This is the preferred option to the Co-Rapporteur. The UK proposes yet another way to restrict the indication, one that is based on the NICE recommendations. Treatment with antidepressants is to be restricted to children and adolescents with moderate to severe depression who were unresponsive to psychological therapy after 4-6 sessions. In addition, antidepressant treatment should only be offered in combination with concurrent psychological therapy.

However, rapporteur considers that there is no evidence to support making a distinction between children and adolescents. No evidence was provided that would support the contention of differences in safety and from a theoretical point of view, suicidality would seem to be more of a risk in adolescents compared to children. From the efficacy point of view, the available evidence indicates similar efficacy in the two age groups.

An alternative view is that due to the safety concerns and the lack of evidence to support restriction of treatment to a suitable population in which treatment is effective, there is currently no sufficient support for granting an indication. Nevertheless, this view is in favour of providing the available evidence, with respect to efficacy and safety, in the relevant sections of the product information. **This position is favoured by the Rapporteur as well as by IE,FR and DK.**

However, before a decision can be taken, there is a need for the MAH to clarify their position concerning the safety issues. Additionally, the company will be requested to provide evidence to support a restricted indication. Moreover, a risk management plan should be submitted for use in children. In this RMP, apart from the short-term and long-term safety issues, the MAH should also be asked to address the dose, as a lower dose might be more appropriate.

Recommendation
At the moment there are insufficient data for a positive benefit/risk. The MAH should be invited for a hearing.

Questions to be answered at the hearing and in writing

1. Preclinical and clinical data raise concerns about the long-term safety for children and adolescents particularly related to growth, mental development and sexual maturation. The MAH should discuss how they plan to address these issues and which clinical studies are foreseen. In addition the MAH should discuss the animal studies to be conducted to help answering the clinical safety issues

2. It is unclear which patients would benefit from treatment. The MAH should compare the patients who were included in the trial and the patients not included and discuss the data available for a better definition of the population

3. The MAH is asked to forward a risk Management Plan for the use of fluoxetine in children and adolescents, addressing the various safety issues and the possibility of a lower dose.

Question to be addressed in writing

1. Regarding study B1Y-MC-HCLS - Can the Applicant clarify if there were any differences between cases and controls regarding

   a) Somatic illnesses?
   b) Drug therapies other than psychiatric drugs?
   c) Smoking?
   d) Alcohol use?
   e) Drug abuse?
   f) Socioeconomic status?

Commitments
The company should keep the CHMP informed about the response of the TADS investigators concerning follow up of patients in order to establish long-term effects. If this is negative then, alternative approached to studying long-term (off treatment) effects on growth and development should be proposed. It is recommended that a time schedule for this be set up.

II. COMPANY'S RE SPONSE TO LIST OF OUTSTANDING ISSUES

Pre-clinical aspects

Question 1
As there are clearly difficulties is carrying out clinical studies, data from a juvenile non-rodent (dog) study of sufficient duration and initiated at the appropriate time are needed to evaluate effects on sexual maturation, including testicular effects, and bone development. A study protocol should be submitted.

Company's response: