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

PROZAC (fluoxetine) – Paediatric indication

RAPPORTEURS' ASSESSMENT REPORT
Assessment of MAH Response to CPMP List of Questions

Rapporteur:	Dr. Barbara van Zwieten - Boot
Co-Rapporteur:	Dr. Tomas Salmonson
Arbitration Procedure restart date:	15 September 2005
Date of Preliminary report:	31 October 2005
Deadline for CHMP members' comments:	8 November 2005

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:
Names of the assessors:	Clinical: Name: Tel: Fax: Email: Preclinical Name: Tel: Fax: Email:
EMEA PTL:	Name: Tel: Email:

TABLE OF CONTENTS

I. RECOMMENDATIONS

It is not recommended to grant an indication to fluoxetine for the treatment of depression in children and adolescents because the benefit/risk balance in the claimed indication is deemed negative.

Concerns about safety issues were not resolved, specifically concerns about suicide related behaviours, including suicide attempt and suicidal ideation, and, from non-clinical data, about the effect on growth, sexual maturation, cognitive and emotional development. The limited evidence concerning long-term safety is a concern as well, especially given these safety signals.

Moderate effects, though somewhat inconsistent across trials, were seen, but there are doubts about the external validity of these results due to the stringent selection procedure. In addition, the lack of evidence to support dose recommendations in this young patient population, add to the negative balance regarding this new indication.

II. EXECUTIVE SUMMARY

II.1 Problem Statement

Fluoxetine, an SSRI, is an antidepressant that is registered for the treatment of major depression, obsessive compulsive disorders (OCD), and bulimia nervosa in adults in most EU member states. The Reference Member States (RMS) for Prozac are the UK (for the 20 and 60 mg oral capsules and 20 mg oral solution formulations) and France (for the 20 mg dispersible tablets).

The CHMP advised in April 2005 to include a warning for the class of all serotonin selective re-uptake inhibitors (SSRIs), including fluoxetine, indicating that these products should not be used in children and adolescents except in their approved indications.

A request to extend the indication of Prozac to include treatment of major depression in children and adolescents aged 8 to 17 (only for the 20 mg capsules, the oral solution and the dispersible tablets) was submitted by the company and evaluated in a mutual recognition type II variation procedure with the UK and France as RMS.

In addition to objections that were raised in response to the request, during the course of this procedure new information concerning safety have become available from preclinical as well as clinical studies. Animal studies have raised concerns with respect to effects of early exposure on growth and sexual maturation. A non-company sponsored clinical study (the Treatment of Adolescents with Depression Study (TADS)) demonstrated that fluoxetine, in common with other SSRIs, is associated with increased risk of suicidal behaviours in young persons.

Overall there were unresolved objections and concerns with respect to the following issues:

Efficacy:

- Representativeness of the included patient population.
- The lack of information regarding optimal dose.
- The limited information regarding long-term efficacy.

Safety from clinical studies:

- Higher rates of suicidal related events in the fluoxetine compared to placebo treated patients.
- Concerns about reduced height and weight gain.
- Lack of data concerning effects on maturation, cognition and behavioural development.
- Limited long-term safety data.

Preclinical safety:

- Effects on bone development.
- Effects on sexual development.
- Irreversible testicular toxicity.
- Effects on emotional development.

As these objections were not resolved during the course of the procedure, France initiated a referral for Arbitration on May 2nd 2005 for the capsules and oral solution for which the UK is the RMS. Based on the unresolved objection listed above, 13 questions were formulated to which the company was requested to respond by 29 August 2005. The assessment of these responses can be found below.

The Type II application for the dispersible tablets for which FR is the RMS was refused on May 3rd 2005.

II.2 Non-clinical aspects

Most of the concerns regarding non-clinical issues might have been solved because of the planned clinical studies. A study planned to study the neuroendocrine effects of fluoxetine might be helpful in understanding the endocrine effect on the testis. However, there are important species differences in this respect and it might be questioned whether an additional rodent study will be reassuring the safety in humans although explaining the rodent testicular degeneration at the high dose. Data from non-rodent juvenile study are lacking in this respect to confirm the absence of this type of neuroendocrine effects in conjunction with the absence of testicular effects.
With respect to the bone effects the data in rodents are not predictive for a safety issue in humans. Findings were reported only at a high supratoxic dose. The effects on body weight were found to be stronger than the effects on the femur length.
With respect to the effects on emotional behaviour and the reversibility of effects it would be preferable to have a study regarding these endpoints in children at the age aimed at for the present application circumventing the issue of extrapolation. However it might be difficult or even impossible to carry out such a study in children nowadays. Therefore, further nonclinical data covering the right time window should be present. (see question 5).

As clinical studies cannot solve the issue of the significance of the testicular effects and the delay in sexual maturation there is more emphasis on the lack on data from a non-rodent study (see question 1).

II.3 Clinical aspects

Methodology

Three randomised paediatric clinical trials were assessed. Two of these trials were sponsored by the company (HCJE and X065) and the third was an NIMH sponsored trial – the Treatment of Adolescents with Depression trial (TADS)[1]. An earlier company sponsored pilot study (HCJJ) was terminated early due to slow recruitment. Only 40 patients were recruited into the study of whom 10 dropped out. The scanty report of the study results indicate that fluoxetine was not more efficacious than placebo. This study will not be discussed further in this report.

Essential features of the three trials are summarised in table 1 below. The two company sponsored trials were randomised, double-blind and placebo-controlled. In both trials, a fixed dose of 20 mg fluoxetine was used. In study HCJE a dose of 10mg was given in the first week of the study followed by an increase to 20 mg at week 2. In study X065 patients were started on a 20mg dose. Those who were unable to tolerate fluoxetine 20 mg/day were allowed to take fluoxetine 20 mg every other day (alternate day dosing).

Children and adolescents were included in these trials after they have gone through an extensive assessment period that lasted 3 weeks and included three diagnostic interviews with three different psychiatrists, followed by a 1-2 weeks single-blind placebo lead-in period. Only those patients who met the inclusion criteria at all three interviews and did not respond to the single-blind placebo treatment, were randomised to receive double blind placebo or fluoxetine.

As the table below indicates, in study HCJE this rigorous selection procedure has lead to the exclusion of almost half of the initially recruited children. Of the 420 initially recruited patients, 193 (46%) did not meet inclusion criteria after the assessment period, and an additional 8 (2%) were excluded based on placebo response. For study X065 this information is not provided. The study report only indicates that out of the 108 patients that met diagnostic criteria during the initial assessment period, 12 (11%) either failed inclusion/exclusion criteria after placebo run-in or decided not to participate in the study. It is therefore likely, based on the number of excluded patients in study HCJE, that a much larger group of patients were excluded following the extensive screening and evaluation phase.

The TADS study was a randomised trial in which adolescents were allocated to one of four treatment groups: Fluoxetine alone, placebo, Cognitive Behavioural Therapy (CBT) alone, and a combined treatment of both

[1] March J, Silva S, Petrycki S, Curry J, Wells K, Fairbank J, Burns B, Domino M, McNulty S, Vitiello B, Severe J (2004). Fluoxetine, Cognitive-Behavioral Therapy, and Their Combination for Adolescents With Depression: Treatment for Adolescents With Depression Study (TADS) Randomized Controlled Trial. *JAMA.*;292:807-820.

fluoxetine and CBT. Treatment allocation was blind only in the first two groups (fluoxetine and placebo) and hence only these two groups will be addressed in this report.
Like in the two company sponsored trials, this trial included an extensive screening and evaluation procedure (two diagnostic assessments: at consent and at baseline) which led to the exclusion of the majority of patients who were initially recruited[2].

Table 1. Fluoxetine trials – study design

Study ID	Design	Inclusion	Age range	Dose	Duration	N (chil:adls)	Selected/screened (%)
HCJE	Random. DB Plc. cont.	Non-psychotic MDD (DSM-IV) CDRS-R>40 CGI-S ≥ 4	8-17	1st week: 10 mg/d; next 8 wks: 20 mg/d	9 weeks	219 (122:97)	219/420 (52%)
X065	Random. DB Plc cont.	Non-psychotic MDD (DSM-III-R) CDRS-R>40	8-18	20mg	8 weeks	96 (48:48)	Not reported
TADS	Random. 4 trtmnt: FLX PLC CBT CBT+FLX	MDD (DSM-IV) CDRS-R≥45	12-17	Start w/ 10mg/d; Then increase to 20-40 mg/day	12 weeks	439 FLX 109 PLC 112	439/2804 (15%)

The acute 9 weeks phase in study HCJE was followed by a 10 week sub-acute phase in which non-responders to 20 mg fluoxetine were re-randomized to either remain on fluoxetine 20 mg/day or to receive fluoxetine 40 mg/day with an option to titrate to 60 mg/day at Visit 12. Placebo responders and non-responders remained on placebo and fluoxetine responders remained on fluoxetine (20 mg).

Comment of the assessor
It is difficult to see how blindness can be maintained in this extension part. It would seem that blindness needs to be broken, at least for non-responders.

Fluoxetine responders from this latter study period were entered into a randomised withdrawal study that lasted 32 weeks.

[2] The difference in % patients excluded between HCJE and the TADS can be explained based on the fact that the TADS figure includes the proportion of patients excluded based on a telephone screening while the HCJE figure does not (Like in the TADS, a telephone screening with parents took place in the two company sponsored trials, but the number of excluded patients is not reported). When only the 1088 TADS patients who remained after the telephone interview are considered in the calculation, the proportion selected out of those initially screened is 439/1088= 40%.

Efficacy

The results of the three fluoxetine trials in terms of responders are described in table 2 and in terms of mean change score (from baseline to end of study) in table 3.

The primary outcome variable in TADS was defined as the difference between the treatment groups in slope of the CDRS scores over time. No statistical significant differences between fluoxetine alone and placebo was obtained on this parameter. Analysis of CDRS responders was not presented in the article describing the study results. However, differences in CGI responders (table 2) and in mean change scores on the CDRS (table 3) were statistically significant.
Mean changes on CDRS were in favour of fluoxetine in both X065 and HCJE, but in the latter study there was no difference from placebo in % responders.

Table 2. Fluoxetine trials – results in terms of responders

Study	Placebo	Fluoxetine	Difference (95% CI)	p-value
X065 CDRS responders [a]	15/47 (32%)	28/48 (58%)	26% (6% , 44%)	P=0.013
HCJE CDRS responders	54/101 (53%)	71/109 (65%)	12% (-1.6 % , 24%)	P=0.093 [b]
TADS CGI responders	39/112 (35%)	66/109 (61%)	26% (13% , 38%)	P=0.001

[a] Responders in X065 and in HCJF defined as 30% reduction in CDRS.

[b] The difference is not statistically significant when the efficacy population is used. Efficacy population is define (by the company) as all randomised patients who took study medication, had a baseline measure and at least 2 post-baseline measures. The MHRA assessor re-calculated the rate based on all randomised patients in which case the rate for placebo changes to 54/110=49% and the difference becomes statistically significant (p=0.02).

Table 3. Fluoxetine trials – results in terms mean change from baseline in CDRS

Study	Placebo Mean (SD)		Fluoxetine Mean (SD)		Difference (95% CI)	p-value
	Baseline	Change	Baseline	Change		
X065	57.5 (10.4)	-10.5 (15.9)	58.9 (10.4)	-20.2 (13.5)	9.7 (3.7 , 15.7)	p=0.002
HCJE	55.1 (11.8)	-14.9 (13.3)	57.1 (9.9)	-22.1 (14.4)	7.2 (3.4 , 11.0)	p<0.001
TADS	61.2 (10.5)	-19.4 (9.06)	58.9 (10.2)	-22.6 (9.10)	3.2 (0.8 , 5.6)	P=0.01

Stratified analysis by age (children/adolescents) indicated no difference in effect sizes between these two groups.

The results of the 10-weeks randomised up-titration study in non-responders (n=29) indicate that the group that was uptitrated had improved more compared to the group that remained on 20 mg. However, the difference did not reach statistical significance. In addition, baseline values of CDRS score in the group randomised to be uptitrated were higher (46.9) compared to the placebo group (42.7). Hence there was more room for improvement in the group receiving higher doses. Due to all these limitations, the results of this study remain inconclusive.

The results of the 32-weeks randomised withdrawal study (n=40) in fluoxetine responders at week 19 indicated that 12 of the placebo treated patients (60%) and 6 (34%) of the patients who remained on fluoxetine relapsed. The difference between the group was statistically significant (p=0.046) but with borderline value. In addition, there were 4 fluoxetine treated patients who withdrew from the study due to other reasons without having had a relapse. If these patients were to be included as relapses, the difference between fluoxetine and placebo would not have been significant. Furthermore, relapse definition that was used in this study was unacceptable as it included both a CDRS scores being > 40 and subjective experience of the patient or physician.

Comments about efficacy

The evidence for efficacy of fluoxetine seems mixed - a modest effect that reached significance only in some trials (depending the outcome measure). However, more important is the fact that the patients population that was included in the trials is a highly selected group that is not likely to be representative of the total depressed patient population. This group might be more persistently depressed and more homogeneous compared to the initially screened group. However, there is no evidence to support this or any other differentiating characteristics.

A comparison with paediatric depression trials that were conducted with paroxetine indicates that in these latter trials less rigorous selection procedure were employed and lower percentages of patients were excluded (see table 4 below). Comparison of the results indicate that the percent responders in the active arms are similar in the paroxetine and the fluoxetine trials (see table 4 below), while the percent responders to placebo are generally higher in the paroxetine trials.

These comparisons suggest that efficacy in the fluoxetine trials may depend on the inclusion of a selective patients population (one that has not spontaneously recovered within a period of 3-5 weeks and whose depression persisted in the face of considerable attention). However, the deciding characteristics of this selected group of patients that renders them more responsive to the effect of treatment is not known.

Table 4. Comparison of paroxetine and fluoxetine trials in terms of patients selection and placebo response.

	% patients included (out of screened)	Placebo	Active	p-value
Paroxetine Trials				
329 HAMD responders[a]	Not provided	55%	67%	ns
377 HAMD responders	88%	58%	60%	ns
701 CGI responders	68%	46%	49%	ns
Fluoxetine Trials				
X065 CDRS responders[b]	Not provided	32%	58%	P=0.013
HCJE CDRS responders	52%	53%	65%	P=0.093
TADS CGI responders	15%	35%	61%	P=0.001

[a] HAMD responders defined as ≥50% reduction in baseline HAMD scores
[b] CDRS responders defined as ≥30% reduction in baseline CDRS scores

The company's response indicating that only a small proportion of the initially recruited patients were excluded due to placebo response, does not resolve this issue as more patients were excluded following the extensive assessment procedure (see question 8).

Children and adolescents

Stratified analysis by age (children/adolescents) indicated no difference in effect sizes between these two groups. PK data indicate that given a similar dosage, children have twice the serum levels as adolescents. This difference was largely accounted for by weight.

Table 5. Efficacy results (responders) by age subgroups

Study	Population	Placebo	Fluoxetine	p-value
X065	Age 8 to < 13	9/23 (39%)	15/24 (63%)	p=0.148
	Age 13 to ≤ 18	6/24 (25%)	13/24 (54%)	p=0.075
HCJE	Age 8 to < 13	30/55 (55%)	42/61 (69%)	p=0.128
	Age 13 to ≤ 18	24/46 (52%)	29/48 (60%)	p=0.533
Total	Age 8 to < 13	39/78 (50%)	57/85 (67%)	p=0.038
	Age 13 to ≤ 18	30/70 (43%)	42/72 (58%)	p=0.093

There is only meagre evidence to support dose recommendations. The minimum effective dose might be lower for children and adolescent than for adults. This possibility is supported by the fact that in study HCJE significant effects were obtained already after one week of treatment with fluoxetine 10mg. The pharmacokinetic evidence that was presented by the company indicated that serum levels following a given dosage are proportional to weight. However, evidence about serum levels is insufficient to explore this issue, which should be examined in clinical studies. Furthermore, the suggestion to increase the initial dose from 10mg to 20mg after one week is not acceptable because this does not allow sufficient time for a response to occur (see question 6).

Safety

Safety results show a higher rate of suicidal related behaviours in the fluoxetine treated patients (12/270=4.4%) compared to placebo (5/266=1.9%). Although the difference between the two groups is not statistically significant, this is a concern because also non-significant increases in this relatively rare event might represent a serious risk. It perhaps worthwhile to remember that in the review of the use of all SSRIs in children and adolescents which gave rise to the inclusion of a warning concerning suicidality, significant results where only obtained when all depression studies where combined. This is due to the fact that studies are powered to demonstrate efficacy, but are not powered to detect differences in a rare event such a suicidality.

In addition, there are concerns about the effect of treatment on growth (from clinical trials) and on growth and sexual maturation (from pre-clinical studies). Fluoxetine treated patients had slower growth in terms of height and weight compared to placebo treated patients (although the differences decreased with continued treatment).
Manic reactions and decrease in alkaline phosphatase are new adverse events that appeared in the paediatric studies and were not observed in adult studies.

Additional concern included the lack of evidence regarding long-term effects on safety including effects on cognition, learning and development and emotional development.

The limited evidence concerning long-term safety is concerning. Although according to the depression guidelines, long-term effects on learning, development, growth and sexual function may be studied post marketing, the protocols for these studies should be available before licensing. (see question 7). Moreover noting the discussion on these issues in the non-clinical assessment, this is becoming more than a theoretical concern and should therefore be addressed adequately.

Suggestions to carry out clinical studies to elucidate safety issues are rejected by the company as not feasible. Specifically, in response to the suggestion to study testicular toxicity in young humans, it is argued that a physical exam to estimate testicular volume will be unacceptable to patients, parents and investigators and is, in addition, not likely to be approved by ethical review boards.

In response to concerns about delayed growth and sexual maturation the company reports on a planned post-marketing study that was developed as a commitment to the FDA (study HCLY). However, due to the negative publicity about SSRIs, the company now foresees recruitment problems with respect tot this study and claims it is unrealistic to expect that the study could be finalised within the requested time frame. It is therefore proposed to revert instead to results of a retrospective study that have become available in May 2005. However, the results of this study are not presented. Results from the company's adverse event data-base with respect to delays in growth and maturation are presented but are rendered as inconclusive. (see question 10).

Altogether, little information is provided that could alleviate the concerns with respect to these safety issues. In addition, the responses that were presented do not provide any assurance that these issues will be explored in the future by the company.

Conclusion

The available evidence indicates that the efficacy of fluoxetine is modest but that there is a concern with regard to the external validity of the results which limits generalizability.

There is no evidence to support making a distinction between children and adolescents, based on the limited data, although PK data indicate that the younger/lighter children may be overdosed.

In addition to the limited efficacy results, the lack of evidence to support dosing, especially minimal effective dose, is concerning as safety parameters may be related to dose. The company suggest to address this in the SPC, but at the moment the data do not support a proposal for dosing; especially in the younger children more data would be needed.

In the face of the limited efficacy results, safety concerns are all the more salient. Increased risk for suicide related behaviours emerged as the most concerning safety finding from the clinical trials. Other safety concerns include effects on growth and sexual maturation including effects on fertility, and effects on cognitive and emotional development. Although some of these effects emerged from pre-clinical studies and hence generalizability to humans is an issue, there seems little reasons to disregard these evidence and few possibilities to verify the risk in human as recruitment to such studies is becoming difficult under the current public attention and concern to these issues.

Therefore, it is not recommended to licence the indication of depression in children and adolescents as the benefit/risk balance cannot be viewed as positive. The warning in 4.4 should be maintained as for all SSRIs; the results of the studies could be summarised in section 5.1 The company should be encouraged to conduct further trials, concerning the dose, the efficacy in a more general population and concerning long-term safety. For the latter adequate animal models might be needed.

II.4 SPC assessment

Proposed changes and additions to the SPC that are relevant for the paediatric indication are assessed below (other changes to the SPC will be discussed elsewhere).

4.1 Therapeutic indications

Children and adolescents aged 8 years and above:
Moderate to severe major depressive episode.

ASSESSORS' COMMENT

It is not recommended to grant this additional indication as the efficacy/safety balance for the paediatric population is not positive.

4.2 Posology and method of administration

Children and adolescents aged 8 years and above:
Treatment should be initiated and monitored under specialist supervision. The starting dose is 10mg/day given as 2.5ml of the Prozac liquid formulation. Dose adjustments should be made carefully, on an individual basis, to maintain the patient at the lowest effective dose.
After one week, the dose may be increased to 20mg/day. Clinical trial experience with daily doses greater than 20mg is minimal. There is only limited data on treatment beyond 9 weeks.
Lower weight children:
Due to higher plasma levels in lower weight children, the therapeutic effect may be achieved with lower doses (see Section 5.2 Pharmacokinetic properties).
For paediatric patients who respond to treatment, the need for continued treatment after 6 months should be reviewed. However, if no clinical benefit is achieved, treatment should be discontinued and alternative treatments considered.

ASSESSORS' COMMENT

There is no sufficient evidence to support dose recommendation. Lower doses compared to adults may be necessary in children and adolescents (see also comment with respect to question 6). The proposal allowing dose increase after one week is not acceptable because a longer time is needed for a response to occur. Steady-state plasma levels will only be achieved after 20-30 days for fluoxetine and nor-fluoxetine.

4.4 Special warnings and special precautions for use

Use in children and adolescents under 18 years of age
Prozac should not be used in the treatment of children and adolescents under the age of 18 years except for moderate to severe major depressive episodes in children and adolescents aged 8 years and above. Suicide-related behaviours (suicide attempt and suicidal thoughts), and hostility (predominantly aggression, oppositional behaviour and anger) were more frequently observed in clinical trials among children and adolescents treated with antidepressants compared to those treated with placebo. If, based on clinical need, a decision to treat is nevertheless taken, the patient should be carefully monitored for the appearance of suicidal symptoms.
In addition, long-term safety data in children and adolescents concerning growth, maturation and cognitive and behavioural development are lacking.
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.
In paediatric trials, mania and hypomania were commonly reported (see section 4.8). Therefore, regular monitoring for the occurrence of mania/hypomania is recommended. Fluoxetine should be discontinued in any patient entering a manic phase.
It is important that the prescribers discusses carefully the risks and benefits of treatment with the child/young person and/or their parents.

ASSESSORS' COMMENT

The modification of the standard SSRI warning text to allow treatment of depression is not acceptable due to the negative benefit balance in this population.

4.8 Undesirable effects

*Children and adolescents **(see section 4.4 Special warnings and special precautions for use):***
The safety of fluoxetine has not been systematically assessed for chronic treatment longer than 19 weeks.
In paediatric clinical trials, manic reactions, including mania and hypomania, were reported commonly (2.6% of fluoxetine-treated patients vs. 0% in placebo-controls), leading to discontinuation in the majority of cases. These patients had no prior episodes of hypomania/mania.
After 19 weeks of treatment, paediatric subjects treated with fluoxetine in a clinical trial gained an average of 1.1 cm less in height (p=0.004) and 1.1 kg less in weight (p=0.008) than subjects treated with placebo. Isolated cases of growth retardation have also been reported from clinical use.
Isolated cases of adverse events potentially indicating delayed sexual maturation or sexual dysfunction have been reported from paediatric clinical use. (see also section 5.3)
In paediatric clinical trials, fluoxetine treatment was associated with a decrease in alkaline phosphatase levels.
In paediatric clinical trials suicide-related behaviours (suicide attempt and suicidal thoughts), and hostility were more frequently observed among children and adolescents treated with fluoxetine compared to those treated with placebo.

ASSESSORS' COMMENT

The text concerning suicide related behaviours should be moved to the beginning of this section.
The text regarding retardation in growth and sexual maturation should mention that it is not known whether this effect can be reversed once treatment is stopped.

5.1 Pharmacodynamic properties

Major depressive episodes (children and adolescents): Clinical trials in children and adolescents aged 8 years and above have been conducted versus placebo. Prozac, at a dose of 20mg, has been shown to be significantly more effective than placebo in two short-term pivotal studies, as measured by the reduction of Childhood Depression Rating Scale-Revised (CDRS-R) total scores and Clinical Global Impression of Improvement (CGI-I) scores. Response rates (defined by a 30% decrease in the CDRS-R score) demonstrated a statistically significant difference in one of the two pivotal studies. There is only limited data on efficacy beyond 9 weeks.

ASSESSORS' COMMENT

The lack of long-term safety data should be added to this text.

5.2 Pharmacokinetic properties

At-risk populations

Children and adolescents: The mean fluoxetine concentration in children is approximately 2-fold higher than that observed in adolescents and the mean norfluoxetine concentration 1.5-fold higher. Steady state plasma concentrations are dependent on body weight and are higher in lower weight children (see 4.2 Posology and method of administration). As in adults, fluoxetine and norfluoxetine accumulated extensively following multiple oral dosing; steady-state concentrations were achieved within 3 to 4 weeks of daily dosing.

ASSESSORS' COMMENT

If the indication is not accepted then the reference to section 4.2 should be deleted.

5.3 Preclinical safety data

There is no evidence of carcinogenicity or mutagenicity from *in vitro* or animal studies.
In a juvenile toxicology study in CD rats, administration of 30 mg/kg/day of fluoxetine hydrochloride on postnatal days 21 through to 90 resulted in degeneration and necrosis of seminiferous tubules of the testis, epididymal epithelial vacuolation, immaturity and

inactivity of the female reproductive tract and decreased fertility. Following an approximate 11-week recovery period, sperm assessments only indicated an approximately 30% decrease in sperm concentrations without affecting sperm morphology or motility. Microscopic evaluation of testes and epididymides indicated that testicular degeneration was irreversible. The significance of these findings in humans is unknown. Delays in sexual maturation occurred in the 10-mg/kg/day treated males and in the 30-mg/kg/day treated males and females. Femur lengths at 30mg/kg/day increased to a lesser extent compared with control rats. Other findings in rats administered 30 mg/kg included increase of serum activities of creatine kinase (CK) and aspartate aminotransferase (AST), which were accompanied microscopically by skeletal muscle degeneration, necrosis and regeneration. At 10 mg/kg/day, plasma levels achieved in animals were approximately 0.8 to 8.8 fold (fluoxetine) and 3.6 to 23.2 fold (norfluoxetine) those usually observed in paediatric patients. At 3 mg/kg/day, plasma levels achieved in animals were approximately 0.04 to 0.5 fold (fluoxetine) and 0.3 to 2.1 fold (norfluoxetine) the plasma concentrations usually achieved in paediatric patients.

A study in juvenile mice has indicated that inhibition of the serotonin transporter prevents the accrual of bone formation. This finding would appear to be supported by clinical findings. The reversibility of this effect has not been established.

Another study in juvenile mice has demonstrated that inhibition of the serotonin transporter had long lasting effects on the behaviour of the mice. There is no information on whether the effect was reversible. The clinical relevance of this finding has not been established.

ASSESSORS' COMMENT

The text is too detailed and should be condensed.

II.5 DRAFT PROPOSED LIST OF OBJECTIONS/OUTSTANDING ISSUES

Non-clinical aspects

1. The company is planning to do an additional study in rats concerning the hormonal regulation. The data are awaited for. Data on non-rodents e.g. dogs (with a duration long enough to include sexual maturation) are important taken into account the difficulties in getting human data in this respect. Therefore, it is not acceptable that data on sexual maturation in non-rodents are lacking.

2. Rodents are not a good model for the bone physiology of humans, as is well-recognized in the field of pharmacotherapeutics directed to the treatment of osteoporosis. It is clear that a clinical study is difficult to get done. Data from juvenile non-rodent studies of sufficient duration started at the right time might be helpful to evaluate the effects on bone density. These data are lacking.

3. With respect to the effects on emotional behaviour and the reversibility of effects it would be preferable to have a study regarding these endpoints in children at the age aimed at for the present application circumventing the issue of extrapolation. However it might be difficult or even impossible to carry out such a study in children nowadays. Therefore, further nonclinical data covering the right time window should be present.

Clinical aspects

4. The patients that were selected into the fluoxetine trials constitute only a small proportion of the originally recruited patients and are therefore not representative of the total population of depressed children and adolescents. Consequently efficacy results cannot be generalised to the total patients population. Furthermore, there is no indication as to the deciding or essential characteristic of this selected group, which would allow the identification of patients who are likely to respond. Hence there is no basis to limit the indication to depressed patients with certain characteristics.

5. The increased rate of suicide related behaviour in the fluoxetine treated group is concerning. Although the increase is not statistically significant, this is still a crucial concern since even a non-significant increase of this rare, yet severe, adverse event is alarming. It perhaps worthwhile to remember that in the review of the use of all SSRIs in children and adolescents which gave rise to the inclusion of a warning concerning suicidality, significant results where only obtained when all depression studies where combined. This is due to the fact that studies are powered to demonstrate efficacy, but are not powered to detect differences in a rare event such a suicidality.

6. Lack of evidence to support the dose is concerning. The minimum effective dose for children may well be lower than adult doses. Since adverse effects might be related to dose, clinical evidence to support the minimal effective dose is especially important in this dossier where adverse effect are particularly at stake.

7. Effects on growth, maturation, sexual development, including fertility, and on emotional development raise concern. Although there may be doubts about the relevance of the pre-clinical findings to humans, these events are sufficiently concerning especially given the lack of long-term safety data.

III. ASSESSMENT OF RESPONSES TO CPMP LIST OF QUESTIONS

III.1 Non-Clinical

The study on young rats for the assessment of the juvenile toxicity shows a very unfavourable profile to support the paediatric indication of fluoxetine hydrochloride. Severe effects were observed 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.

The adverse effects may be due to exaggerated pharmacological effects (modification of GnRH, neuroendocrine and immulogical parameters). However, the effects are severe and they appear with no or low safety margins. Notably the effects on testes were not reversible and reproductive performances were affected at the top dose. Some effects (delayed growth and delayed puberty) have been reported in humans. The safety margins are lower than those calculated by the MAH, because the MAH based its calculation on LOAELs instead of NOAELs. For example, the NOAEL of 3 mg/kg/day corresponds to an absence of safety margin (less than 1, based on systemic exposure). The reversibility or non-reversibility of the observed effects is a concern, as the clinical observations from clinical studies and from pharmacovigilance database. Therefore the provided data are not currently acceptable for the agreement of a paediatric indication of fluoxetine hydrochloride.

<u>Question 1:</u> Further explanations and studies are necessary to better define the mechanism of each adverse effect observed in juvenile rats, the reversibility of the effects for reproductive toxicity, the effects on the hormonal status, the role of the metabolites (taking into account potential differences in norfluoxetine formation in adults and children, when doing interspecies comparisons) and the rate of metabolization. The interspecies toxicity, especially for testes lesions and sexual maturation should be documented in prospect of the clinical relevance for young human.

COMPANY'S' RESPONSE:

The document "Analysis of male reproductive, skeletal muscle, sexual maturation, and growth effects of fluoxetine and norfluoxetine" contains a detailed review of the concerns outlined above and was included in the March 18th response to the AFSSAPS Final Assessment Report. The overall risk assessment takes into account margins of safety and other factors of equal or greater significance, including the relative sensitivity of monitorable and poorly monitorable (e.g. testicular toxicity) changes. The current data package is considered acceptable in assessing clinical risk; however, to understand the hormonal status surrounding the time of sexual maturation, an additional rat study is planned.

In summary, no toxicities were observed that were unique to the juvenile rats except for the slight delay in sexual maturation, which is an endpoint unique to development and therefore would not be expected to be affected in adults. Subtle delays in the onset of puberty were observed in the juvenile rat study with R,S-fluoxetine. The effects were greater at exposures that exceeded the maximum tolerated dose (MTD); however, interpreting these data is confounded by the clinical condition of the

animals. Although maturation delays were observed at the mid- and high-doses, all rats ultimately reached sexual maturity prior to the cessation of treatment. The clinical relevance of delayed sexual maturation in rats is unclear but is a monitorable event in human subjects. Hormones were not measured in this study; however, other studies examining the neuroendocrine effects of serotonergic compounds suggest that perturbation of GnRH secretion is a possible cause.

An additional rat study is currently planned to further assess the hormonal status during the time of sexual maturation delay. Female rats will be administered fluoxetine at 0, 10, or 30 mg/kg/day from postnatal day (PND) 21 to the end of the study. Various time points will be evaluated from approximately PND 28 to 44 for serum LH, FSH, estradiol, progesterone, prolactin, and inhibin B levels. Vaginal patency and ovarian histology will also be evaluated. Male rats will be given the same doses beginning on PND 21 and continuing until the end of the study. Various time points will be evaluated from PND 28 to 60 for serum LH, FSH, testosterone, inhibin B, prolactin, and androstenedione. Balanopreputial separation (BPS) will also be evaluated. This study will assess treatment-related effects of fluoxetine on the HPG axis and correlate any hormonal, maturational landmark, and/or morphological changes.

Lilly recognizes the low margins of safety based on plasma drug exposures. The table in Attachment 1 summarizes the margins of safety for fluoxetine and norfluoxetine; preadolescents and adolescents, including ranges for individual subjects; and single dose and steady-state values. For the endpoints in the juvenile R,S-fluoxetine study that were only affected at exposures above the MTD (testes and skeletal muscle pathology and femur length), individual margins of safety ranged from 0.4 to 23.For the endpoints that were affected at a lower exposure (body weight gain and sexual maturation), individual margins of safety ranged from 0.1 to 2.1. While the margins of safety based on this rat study are low, dose-response relationships in the rat study suggest that the clinical risk of these events is low. While this rat study might predict an effect on body weight gain or a slight delay in sexual maturation at therapeutic exposures, these are monitorable effects. Any profound toxicity (e.g. irreversible testicular toxicity) occurred only in conjunction with other clinically observable signs of toxicity (e.g. extreme decreases in body weight gain) and at an exposure that is not tolerated chronically in the rat. Current paediatric doses are well-tolerated upon repeated administration and are considered below the pharmacologic challenge required to produce the unwanted high-dose effects described.

Assessor's addition of data to support the discussion.

Comparative pharmacology of R-fluoxetine, S-fluoxetine, R-norfluoxetine, and S-norfluoxetine

Serotonergic effects mediated by inhibition of 5-HT uptake constitute the primary pharmacology of fluoxetine and norfluoxetine enantiomers. S-norfluoxetine is the most potent of the four pharmacologically active enantiomers relative to 5-HT uptake inhibition.

With respect to 5-HT uptake in cortical synaptosomal preparations, Snorfluoxetine is approximately two-fold more potent than R-fluoxetine and S-fluoxetine and approximately 20 fold more potent than R-norfluoxetine (Wong et al., 1993). This relative potency difference is also apparent ex vivo. S-norfluoxetine significantly lowered 5-HT uptake in hypothalamus homogenates with estimated ED_{50} values of 3 mg/kg IP and 4.7 mg/kg SC. In contrast, the ED_{50} values for R-norfluoxetine exceeded 20 mg/kg by either route of administration (Wong et al., 1993). The two enantiomers

of fluoxetine and norfluoxetine are weak inhibitors of NE uptake in rat cortical synaptosomes and weak inhibitors of DA uptake in striatal synaptosomes (Wong et al., 1990, Wong et al., 1993). In addition, these compounds have little affinity for receptors of neurotransmitters, including 5-HT, NE, DA, acetylcholine, and histamine (Wong et al., 1983, Wong et al., 1985). Relative to 5-HT subtypes, R-fluoxetine and R-norfluoxetine are more potent than the S-enantiomers to 5-HT1C receptors in membranes of bovine choroids plexus; however, the affinities for the 5-HT uptake site is two orders of magnitude higher so that the pharmacological relevance of this is unknown.

Juvenile rat study A summary of the most relevant data from the **juvenile rat study** is given in the following tables:

Table 1a Organ weight parameters in the control, 3-, 10- and 30-mg/kg

Dose (mg/kg): a	0	3	10	30
	MALES			
Final Body Weight [G]	467	463	468	346**
Epididymides [G]				
Absolute	1.25	1.24	1.22	1.13
Relative to final body weight	0.269	0.269	0.263	0.327**
Relative to brain weight	61.262	61.479	59.121	56.403
Left Femur Length (mm)				
Absolute	36.7	36.6	36.6	35.4*
Liver [G]				
Absolute	13.61	13.97	14.58	12.95
Relative to final body weight	2.915	3.020	3.097	3.725**
Relative to brain weight	668.284	691.789	701.280	646.176
Testes [G]				
Absolute	3.55	3.43	3.38	3.14
Relative to final body weight	0.764	0.742	0.728	0.915**
Relative to brain weight	174.494	169.680	163.473	156.819

a Vehicle

* $p<0.05$ ** $p<0.01$

Table 1b Organ weight parameters in the control, 3-, 10- and 30-mg/kg

Dose (mg/kg):	0a	3	10	30
	FEMALES			
Final Body Weight [G]	279	270	258	205**
Left Femur Length (mm)				
Absolute	33.3	32.7	32.5	31.4**
Liver [G]				
Absolute	8.24	8.05	7.48	6.59**
Relative to final body weight	2.953	2.992	2.897	3.217*
Relative to brain weight	433.434	423.368	387.914	368.976
Ovaries [G]				
Absolute	0.1016	0.0983	0.0939	0.0478**
Relative to final body weight	0.037	0.036	0.037	0.023**
Relative to brain weight	5.348	5.178	4.880	2.637**
Uterus/Cervix [G] Absolute				
	0.51	0.56	0.59	0.23**
Relative to final body weight	0.184	0.207	0.229	0.107**
Relative to brain weight	26.884	29.180	30.359	12.268**

a Vehicle

* $p<0.05$ ** $p<0.01$

Comment assessor: The tables 1A and B clearly indicate that the 30 mg/kg is above the MTD as the body weight is affected more than 20% in males as well as in females. All deviations in the high dose group should therefore be interpreted with caution.

In the tables 2A and 2B the maturation of the male and female sex landmarks are given and it is clear that these landmarks are already affected in the mid dose.

Table 2A Compound-related effects of fluoxetine administration included delayed acquisition of balanopreputial separation in the 10- and 30-mg/kg males

Dose (mg/kg):	0a	3	10	30
Gender	M	M	M	M
Balanopreputial Separation (PND)	42.0	43.3	44.3**	47.1**
Body Weight at Day of Onset (Grams)	214.7	226.5	234.3**	222.1

a Vehicle
** p<0.01

Compound-related effects of fluoxetine administration included delayed acquisition of vaginal patency in the 10- and 30-mg/kg females.

Dose (mg/kg):	0a	3	10	30
Gender	F	F	F	F
Vaginal Patency (PND)	34.4	35.7	37.6	47.1**
Body Weight at Day of Onset (Grams)	127.4	135.3	143.5*	160.9**

a Vehicle
** p<0.01 * p <0.05

Mating performance was only affected in the high dose group (F0 generation) as is clear from table 3.
Male fertility was decreased in the 30-mg/kg group. The mean number of days between pairing and coitus in the 30-mg/kg group (4.9 days) was prolonged compared to the control group (3.1 days) and the maximum mean value in the WIL historical control data (4.7 days) (WIL is the CRO that has carried out the study). The number of females that were used for mating, but did not come to pregnancy numbered 4, 5, 5, and 8 in the control, 3-, 10- and 30-mg/kg groups, respectively. Based on the decreased sperm concentrations, decreased testicular and epididymal weights and the microscopic findings in the testes and epididymides in the 30-mg/kg group, the increase in the number of 30-mg/kg females that were nongravid is likely due to the males of this group.

Table 3

Dose (mg/kg):	0a	3	10	30
Time to mating (days)	3.1	2.6	2.4	4.9
Male Fertility Index (%)	83.3%	100.0%	85.7%	71.4%

a Vehicle

Sperm motility was not evaluated in five males in the 30-mg/kg group due to insufficient numbers of sperm in the samples. These same five males did not sire

litters during the mating trial. Sperm motility and progressive motility in all compound-treated groups were similar to the control group.

Acoustic Startle Test

Treatment started at PND 21 and was stopped after PND 90 (totally 70 days)

On PND 106, dose-dependent decreases in VMAX were noted in the 3-, 10- and 30-mg/kg males and females compared to the control group across the pooled trial blocks; the decrease in 3-mg/kg females was due to a decrease during the first trial block interval. Similar dose-dependent decreases in VAVE values were noted at all dose levels in males and females. On PND 134, VMAX and VAVE remained decreased in the 30-mg/kg males and females compared to the control group. Because the changes in VMAX and VAVE in the 3- and 10-mg/kg groups did not persist into the PND 134 evaluation, the changes on PND 106 **were not considered adverse**.

On PND 106, compound-related increases in TMAX were noted in the 30-mg/kg group rats. A significant treatment by time interaction effect was observed in the 30-mg/kg males, with the 21-30 and 31-40 trial blocks being increased compared to the control group. A main effect of treatment was also noted in the 30-mg/kg males and females, due to the increases in individual trial blocks throughout the 50-trial session compared to the control group. On PND 134, a main effect of treatment was observed in the 30-mg/kg females, with TMAX being increased compared to the control group. TMAX was unaffected in the 30-mg/kg males on PND 134. Table 4 summarizes the statistically significant differences on acoustic startle response.

Table 4	Acoustic startle response			
Dose (mg/kg):	0a	3	10	30
	MALES			
No. of animals tested	18	20	20	17
PND 106				
Vmax (Millivolts)				
All trials	489.0	296.6*	250.3**	117.8**
Tmax (Milliseconds)				
Trials 21-30	32.7	32.8	32.0	43.6**
Trials 31-40	31.8	34.8	33.3	44.0**
All trials	33.0	34.1	32.0	40.2**
PND 134				
Vmax (Millivolts)				
All trials	605.4	405.1	539.1	250.3**
a Vehicle.				
* $p<0.05$ following repeated measures analysis				
** $p<0.01$ following repeated measures analysis				
Dose (mg/kg):	0a	3	10	30
	FEMALES			
No. of animals tested	20	20	18	20
PND 106				
Vmax (Millivolts)				
All trials	194.4	165.4	138.6	90.3**
Tmax (Milliseconds)				
All trials	30.4	30.3	32.6	36.2**
PND 134				
Vmax (Millivolts)				
All trials	253.1	195.8	199.7	93.7**
Tmax (Milliseconds)				
All trials	28.8	30.6	31.5	37.2**
a Vehicle.				
** $p<0.01$ following repeated measures analysis				

Table 5. Margins of Safety: Fluoxetine and Norfluoxetine Plasma Exposures in Preadolescents (6-12 yrs) and Adolescents (13-18 yrs) relative to Juvenile Rats in Study WIL353039

		Fluoxetine				Norfluoxetine			
	Daily dose	Single dose AUC	EM[a]	Steady State AUC	EM[a]	Single dose AUC	EM[a]	Steady State AUC	EM[a]
Human – Preadolescents									
Therapeutic dose	20 mg	NA	NA	4,102[b] (672-7,488)	NA	NA	NA	4,680[b] (1,632-7,440)	NA
Rat – Juvenile[c]									
NOAEL	3 mg/kg	446	0.1 (0.1-0.7)	333	0.1 (.04-0.5)	1,355	0.3 (0.2-0.8)	2,428	0.5 (0.3-1.5)
Minimally toxic dose	10 mg/kg	3,359	0.8 (0.4-5.0)	5,922	1.4 (0.8-8.8)	4,935	1.1 (0.7-3.0)	26,680	5.7 (3.6-16.3)
Exceeding MTD	30 mg/kg	17,575	4.3 (2.3-26.2)	19,764	4.8 (2.6-29.4)	10,254	2.2 (1.4-6.3)	68,474	14.6 (9.2-42)
Human – Adolescents									
Therapeutic dose	20 mg	NA	NA	2,071[b] (720-4,872)	NA	NA	NA	2,700[b] (1,152-3,912)	NA
Rat – Juvenile[c]									
NOAEL	3 mg/kg	446	0.2 (0.1-0.6)	333	0.2 (0.1-0.5)	1,355	0.5 (0.3-1.2)	2,428	0.9 (0.6-2.1)
Minimally toxic dose	10 mg/kg	3,359	1.6 (0.7-4.7)	5,922	2.9 (1.2-8.2)	4,935	1.8 (1.3-4.3)	26,680	9.9 (6.8-23.2)
Exceeding MTD	30 mg/kg	17,575	8.5 (3.6-24.4)	19,764	9.5 (4.1-27.5)	10,254	3.8 (2.6-8.9)	68,474	25.4 (17.5-59.4)

Abbreviations: AUC = area under the curve (ng•hr/mL), EM = exposure multiple, NA = not applicable, NOAEL = no-observed-adverse-effect-level, MTD = maximum tolerated dose.

a. Single-dose exposure multiple = single dose rat AUC/steady state clinical AUC; Steady-state exposure multiple = steady state rat AUC/steady state clinical AUC.
b. Data from Study B1Y-MC-HCIU. Only single time points were collected in this study, so AUCs were approximated by plasma concentration at steady state times 24 hrs. Presented as mean (minimum – maximum) values.
c. Data from study WIL 353039. Adverse changes at the "minimally toxic dose" limited to decreased body weight gain (females only), delayed sexual maturation, and increased serum activity of creatine kinase (females only). Adverse changes observed above the MTD include convulsion, hypersensitivity to touch, hard muscle tone, decreased body weights (25% relative to control) and food consumption, delays in sexual maturation, increased serum activity of creatine kinase, aspartate aminotransferase, and alanine aminotransferase, degeneration and necrosis of skeletal muscle and testes, epididymal vacuolation, immaturity and inactivity of the female reproductive tract, and decreased femur length (relative to control).

ASSESSORS' COMMENT

The company referred to the document "Analysis of male reproductive, skeletal muscle, sexual maturation, and growth effects of fluoxetine and norfluoxetine", that was provided to the authorities in the MRP procedures. This document gives a review of all the data as was requested and the relevant data are summarized in the response of the company given above. Furthermore we have added details from the juvenile rat study to show that the dose response data with respect to the basic endpoints such as body weight gain and gender landmarks.

From these data it is clear that the 30 mg/kg can be characterized as above the MTD (see comment under table 1A and B).

The formation of the active metabolite norfluoxetine is much higher in rodents compared with humans. The pharmacological profile (5-HT-reuptake inhibition is generally the same, but the potency of the metabolite is 2-fold higher). The safety margin should therefore be corrected for the contribution of the metabolite.

The discussion on the differences between the NOAEL and the LOAEL is not very helpful. The choice of the interval of the dosages in the animal studies (3, 10 and 30 mg/kg) and the non-linearity of the formation of norfluoxetine is the reason that the LOAEL is a more relevant measure than the NOAEL, as the exposure at the low dose is too low, whereas the exposure at the next higher dose is much higher than in humans.

As the irreversible activity (testis degeneration) is seen only at the high dose (with an exposure multiple of 25 for the active metabolite) we agree with the company that this irreversible toxicity is not relevant to the human situation. Effects of fluoxetine on fertility of the mouse have been reported already at the stage of marketing application (1989). Hypospermatogenesis was reported in a 3 months study in mice treated with a dose of 31 mg/kg/day, which dose was clearly characterized as above the MTD because of the high rate of deaths in the group.

In the mid dose group sexual maturation is delayed to a small extent, but not absent.

It is well-known that metabolic effects occur also for methylphenidate. In the early pharmacodynamic information fluoxetine was reported to have appetite-decreasing effects, and anorexia was reported consistently for repeat-dose toxicity studies of various duration.

The additional rat study to study the endocrine effects is welcomed although the choice of only 2 dosages is not promising for strong conclusions with regard to a safety margin.

Data in non-rodents might be important too. It is known that hormonal regulation in non-rodents might be quite different from that of rodents. In the 12-months dog studies no effects on the testis have been reported, but the study started at an adult age of the animals. Studies on rhesus monkeys might have been too short (14 days) to provide reassurance that this species is not sensitive to this testicular effect of fluoxetine.

Data on non-rodents are important taken into account the difficulties in getting human data in this respect. Therefore it is not acceptable that data on sexual maturation in non-rodents are not present.

Question 2: The MAH argues that norfluoxetine is implicated in the testicular toxicity. According to the toxicokinetic data, it appears that norfluoxetine exposure at day 21 is approximately 6 to 7 times less than the exposure at day 90. Nevertheless, the testicular toxicity may occur before the day 90, where exposure to norfluoxetine in the rat is lower and, thus, safety margins are lower.

The MAH indicates that the development of testicular pathology in rodents was observed when animals were dosed beginning at 3 weeks of age (R, S- fluoxetine juvenile study) (Lilly research laboratories). In the juvenile study, IGS CD rats (3 weeks of age at initiation) were treated by gavage with 30 mg/kg/day for approximately 70 days. Seminiferous tubule degeneration was observed histologically in 7 of 10 males; however, no gross observations were made. In the one-month study with S-norfluoxetine, dietary exposures resulting in doses of approximately 30 mg/kg/day caused testicular degeneration in 6 of 15 rats. In both studies, the effect doses caused other concomitant clinical signs of toxicity.

As in both studies animals were exposed to S-norfluoxetine, it is considered that S-norfluoxetine is sufficient to induce testicular toxicity. Although the testicular toxicity may be linked to the pharmacological activity of fluoxetine and derivatives, these studies do not demonstrate that S-norfluoxetine is not necessary. A clear characterisation of the testicular toxicity should be investigated with the available data. (see also Q9)

COMPANY'S' RESPONSE:

Characterisation of the testicular toxicity has been included in previous submissions. Briefly, testicular effects were observed in the rat and the mouse, but not in the dog. The testicular findings in the rat and the mouse have been variably described across the studies but all are considered outcomes of the same pathogenesis. The lesion in the 3-month mouse study was described as focal hypospermatogenesis. Across the repeat-dose rat studies, the effects were described as seminiferous degeneration and testicular degeneration. The infrequent and minimal testicular findings in the dog with R,S-fluoxetine or S-norfluoxetine were consistent with background findings (Rehm 2000; Foley 2001) and were not regarded as treatment-related.

As stated in the response to Question 1, an additional rat study is planned to investigate the impact of fluoxetine on the HPG axis (hormonal assessments) in the male. Following daily administration of fluoxetine beginning on PND 21, LH, FSH, testosterone, prolactin, inhibin B, and androstenedione will be assessed on approximately PND 28, 40, 50, and 60. Data from this study may provide additional information relative to understanding testicular changes.

ASSESSORS' COMMENT

The CHMP question is focused on the active metabolite per sé, whereas the company indicates that the pharmacological effect of the drug (and its metabolite) is responsible. In the Rapporteur's view the data from the company are now reassuring, although they might not have been in an earlier stage. The company did not provide

additional data, but there is no need for further histopathological data. The study on the impact of fluoxetine on the HPG axis is welcomed (see question 1)

Question 3: ***General toxicity profile comparison adult – juvenile animals: One aim with juvenile toxicity studies is to assess whether young animals are more sensitive to an effect of a compound than adult animals. Such comparison appears to be lacking. The MAH should present comparisons of the toxicity profile in adult and juvenile rats. Moreover, these profiles should be discussed relative to exposure margins in adults and children, and thereby provide an evaluation whether toxicity profiles are similar in adult and young animals as well as whether there are differences in sensitivity.***

COMPANY'S' RESPONSE:

The relative sensitivity of adult and juvenile rats for the most prominent toxicities observed in animal studies was discussed in a document previously provided to the EU regulatory agencies ("Analysis of male reproductive organ, skeletal muscle, sexual maturation, and growth effects of fluoxetine and norfluoxetine"; dated 18 March 2005; see Appendix 1). The relevant discussion surrounding testicular toxicity, skeletal muscle toxicity, and effects on growth is excerpted below. The studies used in this analysis were conducted over a 28-year period and incorporated mice, three strains of rat, and the beagle dog. R,S-fluoxetine and S-norfluoxetine (two different salts) were studied via diet, gavage, or capsule (studies are listed in Attachment 2). Based on these data, it is apparent that the juvenile animals are not unusually sensitive to the primary toxicological effects of fluoxetine on an exposure:response basis. This observation, coupled with similar pharmacokinetic profiles in juvenile and adult humans, suggests that a meaningful shift in margin of safety is not expected when considering the juvenile population, compared to adult populations. Of note, the margins of safety that have been calculated for this submission are based on juvenile animal data and juvenile human exposure information.

Testicular Toxicity

Important age-related differences in sensitivity are not apparent for testicular toxicity. The development of testicular pathology in rodents has been observed when animals were dosed beginning at 3 weeks of age (R,S-fluoxetine juvenile study) or 6 to 7 weeks of age (S-norfluoxetine one-month study) (Beck 2004; Vodicnik and Roesner 1990). In the juvenile study, IGS CD rats (3 weeks of age at initiation) were treated by gavage with 30 mg/kg/day for approximately 70 days. Seminiferous tubule degeneration was observed histologically in 7 of 10 males; however, no macroscopic observations were made. In the one-month study with S-norfluoxetine, dietary exposures resulting in doses of approximately 30 mg/kg/day caused testicular degeneration in 6 of 15 rats. In both studies, the effect doses caused other concomitant clinical signs of toxicity. The only other rat study conducted at this or greater dose was a 3-month study conducted via dietary administration in 4 to5 weeks of age Harlan-Wistar rats (Wold et al. 1976). All rats receiving approximately 75 mg/kg/day died by Week 9. Minimal testicular immaturity was described in 1 of 10 rats (an early death animal). While the date of the study (reported in 1976), the dietary route, and

the lack of plasma exposure data make it difficult to compare to the other studies above, it seems clear that particular sensitivity to testicular pathology was not observed in these 4 to 5 weeks of age rats.

Skeletal Muscle Toxicity

The development of skeletal muscle pathology is not unique to the juvenile rat and there does not appear to be a particular sensitivity in immature animals. In the juvenile R,S-fluoxetine rat study where 3 weeks of age rats were administered R,S-fluoxetine daily for 70 days, a mean plasma exposure of 3.677 µg/mL (fluoxetine plus norfluoxetine) resulted in 19 of 20 male and female rats having skeletal muscle degeneration and necrosis (Beck 2004). In the mid-dose group where exposures were approximately 1.4 µg/mL, serum CK values in females were slightly increased but no myopathy was observed. In contrast, myopathy was observed with high frequency in a series of studies with S-norfluoxetine in 6 to 7 weeks of age rats with exposure of approximately 1 µg/mL (Vodicnik and Roesner, 1990; Vodicnik and Snyder, 1990). Examining the effect of age on the development of myopathy is confounded by different strains of rats and different test materials among the studies conducted.

Growth Effects

The effects of fluoxetine on juvenile and adult body weight appear comparable on an exposure:response basis. While skeletal growth was only measured in the juvenile rat so that comparison to adults is not possible, it would be expected that effects on the lengthening of long bones would be most prominent during the rapid growth phase in rodents

ASSESSORS' COMMENT

We agree with the comments of the company that the data as presented do not support a difference in sensitivity between juvenile and adult animals. The dose-response data are insufficient to take a firm conclusion on this point. The calculations of the MOS in the MR procedure were suggestive for a difference in sensitivity, but this was caused by differences in exposure in children and adults.

The question is solved.

***Question 4:** Effects on bone accrual and the reversibility of these effects, need to be addressed. This should include a review of available non-clinical and clinical data. Further non-clinical and/or clinical investigations should be proposed.*

COMPANY'S' RESPONSE:

Preclinical data

Effects of fluoxetine on bone mineral accrual have not been studied preclinically by Lilly but the reviewers may be aware of a report in 4 weeks of age mice demonstrating an effect of fluoxetine on bone mineral content in the weight-bearing, but not non-weight bearing bone (Warden et al. 2005). Based on this distribution, hypo activity in the affected mice may have contributed to mineral density changes in this group. The literature also contains preliminary reports suggesting an effect of selective serotonin reuptake inhibitors on bone mineral density in adult humans (Diem et al. 2004; Haney et al. 2004). However, other reports indicate that depression may be an independent risk factor associated with decreased bone mineral density or osteoporosis (Michelson et al. 1996; Schweiger et al. 1994). It is Lilly's position that further animal studies will not meaningfully contribute to the risk assessment of skeletal health in humans and are not warranted. Fundamental differences in bone physiology between rodents and humans (Kimmel 1996) limit the ability of rodent studies to accurately predict the response in the human skeleton. Human skeletal health is monitorable in the clinic and remains a focus of clinical investigation. Information regarding a study which is currently being developed to investigate the effects of fluoxetine treatment in paediatric patients (HCLT) can be found in the Lilly's response to Question 10. Lilly has demonstrated that fluoxetine, at a dose exceeding the MTD, decreased femur length in a juvenile rat study (Beck, 2004). The decreased femur length suggests an effect on longitudinal bone growth; however, this effect was likely reflective of decreased growth secondary to the decreased nutritional status of the animals. While direct or neurohormonal influences on skeletal growth cannot be ruled out, the concurrent decreases in food consumption and body weight are sufficient to be causative. At the dose where a 4 to 6% decrease in femur length was observed, body weights were decreased 24 to 27% relative to controls. Food consumption was also decreased in this group by approximately 25 to 34%. In dietary restriction studies (no fluoxetine treatment), weanling male Wistar rats had decreased femur lengths when their feed was restricted by 20% relative to ad libitum-controls (Boyer et al. 2000). Similarly, male Sprague-Dawley rats subjected to 40% food restriction had decreased femur length (Anugwa and Pond 1989).

Clinical data

The literature contains reports suggesting an effect of SSRIs on bone mineral density in adult humans, but other reports indicate that depression may be an independent risk factor for reduced bone mineral density. The company argues that this issue should be further investigated using studies in humans as animal studies cannot contribute meaningfully to this issue due to limited feneralizability from the animals model. The currently developing protocol of study HCLT is proposed as potentially contributing evidence to this issue.

ASSESSORS' COMMENT (NON-CLINICAL)

We agree with the comments of the company that rodents are not a good model for the bone physiology of humans. This is well-recognized in the field of pharmacotherapeutics directed to the treatment of osteoporosis. Clinical investigations are announced to start under Question 10 (see below). However, it is clear that such a study is difficult to get done. Data from juvenile non-rodent studies of sufficient duration started at the right time might be helpful to evaluate the effects on bone density. These data are lacking.

ASSESSORS' COMMENT (CLINICAL)

As is indicated in the response to question 10, there are grave doubts about the possibility of actually conducting the study due to anticipated difficulties in recruitment. The company in fact proposed to refer to the results of a retrospective study (HCLS) instead of carrying out the previously planned clinical trial (HCLT). Hence the proposal to study the effect of fluoxetine on bone accrual within this study does not seem a realistic option.

Question 5: Effects on emotional behaviour and the reversibility of effects, need to be addressed. The MAH should, taking into account all available non-clinical and clinical data, discuss whether potential effects on brain development and function are adequately addressed, or whether further data can be obtained.

COMPANY'S' RESPONSE:

Lilly considers the current no-nclinical data package acceptable for the assessment of potential effects on brain development and function. The juvenile rat study included a comprehensive evaluation of brain development and function designed to investigate potential effects on CNS development during human childhood through adolescence. Evaluations included sensory and motor functions, learning and memory in a complex water maze, and brain histopathology. Although subtle decreases in startle amplitude were noted 2 weeks after completion of fluoxetine treatment, there were no differences when rats were retested 4 weeks later. There were also no changes in latency to respond to auditory startle at either evaluation. Nonreversible changes in startle and learning (females only) only occurred in conjunction with severe systemic toxicity, and thus, the persistent effects on startle are confounded by the clinical condition of the animals (Beck 2004).

Although a recent study reported long lasting behavioural changes after fluoxetine treatment in 5-HTT+/+ and 5-HTT+/- mice (Ansorge et al 2004), the clinical relevance of these findings for childhood exposure is questionable. In that study, 5-HTT+/+,5-HTT+/-, and 5-HTT-/- mice were administered saline or fluoxetine from postnatal day (PND) 4 through 21. This period of brain development is considered equivalent to a human third trimester fetus through a 2-year old child (Anderson 2003; Bayer et al. 1993; Kimmel and Buelke-Sam 2001; Rice and Barone 2000; Rodier 1980) and does not replicate the recommended age range for fluoxetine administration. Information regarding a study which is currently being developed to

investigate the effects of fluoxetine treatment in paediatric patients (HCLT) can be found in Lilly's response to Question 10.

ASSESSORS' COMMENT

We agree with the comments of the company that the effects on the startle response are small and reversible at a reasonable dose. The rats were tested also in a maze and no statistically significant results were reported. Effects were mainly (although not exclusively) in the high dose group. Dosages leading to an extensive weight loss cannot be trusted to lead to relevant conclusions.

Furthermore, we agree that the study in genetically different strains of mice is not focused on the right time window. It does not exclude, or even might suggest that at higher age these effects might be present and also might be relevant.

It would be preferable to have a study regarding these endpoints in children at the age aimed at for the present application circumventing the issue of extrapolation.

However, as indicated under Question 10, it might be difficult or even impossible to carry out such a study in children nowadays. Therefore, further nonclinical data covering the right time window should be present.

III.2 Clinical Efficacy

Question 6: ***The proposed posology is not sufficiently supported by the submitted documentation. The following concerns should be addressed by the MAH:***

- ***The minimal effective dose has not been established. A lower dose may be equally effective. This may be of particular concern in slow metabolisers. The MAH should discuss and propose ways to study this further.***
- ***The maximum recommended dose should be specified.***

COMPANY'S' RESPONSE:

A recent pharmacokinetic study of fluoxetine in children and adolescents has shown that when given 20 mg fluoxetine children had twice the serum level of fluoxetine and its major metabolite norfluoxetine compared to adolescents, and that this was largely explained by differences in weight.

Based on these results it is proposed to change the dose recommendations in the SPC as follows:

"Children and adolescents aged 8 years and above: Treatment should be initiated and monitored under specialist supervision. The starting dose is 10 mg/day given as 2.5 ml of the Prozac liquid formulation. Dose adjustments should be made carefully, on an individual basis, to maintain the patient at the lowest effective dose. After one week, the dose may be increased to 20 mg/day. Clinical trial experience with daily doses greater than 20 mg is minimal."

ASSESSORS' COMMENT

There are several objections to the solution proposed by the company:

- Pharmacokinetic evidence is insufficient to establish the minimum effective dose since it is known that there is no clear relationship between plasma levels and efficacy (see also ICH E11). Hence, minimum effective dose should be clinically demonstrated. This is particularly important because high exposure in young children may give rise to adverse events: e.g. agitation is thought to be dose related. Furthermore, the results of study HCJE show that improvement of depression symptoms already occurred when 10 mg dosage had been administered for only one week, indicating that 10 mg dose may be effective.
- The SPC proposal allowing dose increase after one week is not acceptable because a longer time is needed for a response to occur. Steady-state plasma levels will only be achieved after 20-30 days for fluoxetine and nor-fluoxetine.
- The issue of slow metabolisers in paediatric patients was not addressed by the applicant, although this was requested.
- Regardless the outcome of this referral, information concerning paediatric pharmacokinetic data should still be included in section 5.2 of the SPC.

Question 7: ***Efficacy has not been formally established for prolonged treatment duration, in particular due to the high number of withdrawals after 9 weeks of treatment. Results on maintenance of efficacy can only be considered as exploratory, due to the small number of patients (about 75) and the dual definition of relapse criteria. The MAH should comment.***

COMPANY'S RESPONSE

The following SPC wording is proposed:

"There is only limited data on treatment beyond 9 weeks."

ASSESSORS' COMMENT

This response does not resolve the problem of lack of long-term evidence with respect to safety. Although according to the depression guidelines, long-term effects on learning, development, growth and sexual function may be studied post marketing, the protocols for these studies should be available before licensing. Therefore, the additional text can be accepted but, in addition, the company is required to submit a study protocol to investigate long-term safety.

Question 8: ***The patients in the pivotal studies were highly selected. The placebo-run-in phase in study HCJE led to the exclusion of 50% of the initially recruited patients. This raises concern with regard to the external validity of the results. The MAH should comment.***

COMPANY'S RESPONSE:

Study HCJE included a 2-week diagnostic evaluation period followed by a 1-week single blind placebo run-in period. Of the 420 patients who entered the study, 201 either decided not to participate in the study or were considered screen failures but only 8 of these 201 were excluded a placebo responders during the placebo run-in period. Thus most patients were excluded due to not meeting inclusion criteria at three different independent evaluations. For the 219 patients who entered the study the mean CDRS-R score was 56 (inclusion criterion required CDRS-R > 40).

The proposed restriction to "patients who failed to respond to psychosocial interventions" is not acceptable to the company as the study did not include specific psychosocial intervention during the screening period. Therefore the company believes that the results are generalizable to all children and adolescents who are diagnosed with major depressive disorder.

ASSESSORS COMMENT

The long and extensive evaluation period (i.e. 2 weeks and 3 different evaluations by three different psychiatrists and not only the placebo run-in period may have led to improvement in patients who were initially depressed and hence to their exclusion

from the study. Although the study did not include a specific psychosocial intervention, the extensive evaluation may have had a similar influence on patients condition. It is difficult to imagine that no encouragement, support and empathy are offered during the course of assessment with a depressed child. In addition, the passage of time (i.e. three weeks) may have brought about spontaneous improvement and, furthermore, in the course of this time other supportive interactions may have taken place. The fact that the mean CDRS-R score of the patients who remained in the study was 56 (and hence considerably higher than the threshold of 40) supports the contention that patients who remained depressed after three assessments were more severely and persistently depressed than the originally recruited patients. Therefore, the concern remains about the applicability of the results to the general depressed patients population.

III.3 Clinical safety

Question 9: ***According to the MAH, the nor-fluoxetine metabolite is implicated in testicular toxicity in young rats. Furthermore, there may be differences in metabolism (e.g. norfluoxetine formation) in adults and children. The MAH should discuss this in relation to the benefit/risk in this population. Additional studies should be proposed in order to explore the risk of testicular toxicity in young humans.***

COMPANY RESPONSE:

A planned study in young male rats was addressed in the response to question 1.

The possibility of different metabolism in adults and children effecting norfluoxetine formation is not addressed by the company.

The company rejects the request to study the risk of testicular toxicity in young humans as not feasible. It is argued that the inclusion of a manual exam to estimate testicular volume, will make such a study unacceptable to patients, parents and investigators. Parents are not likely enrol their children in such a study, given the concerns about suicidality and potential impairment of reproductive function.

In addition, practical limitations in executing such an exam are foreseen. Psychiatrists are not likely to agree to perform a manual exam and if other specialist are recruited for this purpose, this will increase the inconvenience to patients and parents. In addition it is argued that such a test will not provide reliable results, especially in young males who have not developed hormone levels that are amenable to testing.

In addition, such a study is not likely to pass the review of most Ethical Review Boards due to the perceived risk with respect to suicidality and potential impact on testicular toxicity, growth and maturation.

ASSESSORS COMMENT

The possibility of different metabolism in adults and children effecting norfluoxamine formation is not addressed by the company.

It is accepted that a randomised controlled trial in children and adolescents which is aimed at assessing testicular toxicity is not feasible. However, the difficulties that are expected in recruiting patients to such study attest to the wide spread general concern about the use of fluoxetine to treat paediatric patients and may suggest that granting an indication for this population would be difficult to justify based on safety concerns.

Question 10: ***It is considered that the clinical relevance of toxicological data from study in juvenile rats cannot be established at this time. However, some effects (delayed growth and delayed puberty) have been reported in humans: During clinical trials conducted with fluoxetine in children and adolescents, statistically significant differences in height gain and/or weight gain have been observed between treatment groups, with a smaller gain in fluoxetine-treated patients compared to placebo-treated patients. In addition, the examination of all spontaneous reports from MAH database regarding Prozac use in the paediatric population shows 16 cases of growth retardation, 6 cases of delay in puberty (associated in 4 cases with growth retardation), 18 cases of menstrual disorders and 4 cases of sexual disorders. Even though the responsibility of fluoxetine is difficult to assess with accuracy in some cases, in particular due to the lack of information on the outcome, other cases (suggestive chronologies, positive dechallenges) suggest that fluoxetine may have consequences on growth/puberty in treated children and adolescents. These data are representing a signal which cannot be ignored. The MAH should comment.***

COMPANY RESPONSE:

The company reports on a study protocol (HCLT) that has been developed as a phase IV commitment to the FDA since the beginning of 2003. The purpose of this study is to examine the effects of fluoxetine treatment on height and weight development in children and adolescents. The study was planned to recruit 440 children and adolescents with MDD. The design included a screening phase, a acute double blind placebo controlled phase lasting 8 weeks, a 44 weeks double-blind extension phase in responders, and a 52 weeks follow-up phase. Outcome variables include height, weight, Tanner breast/genital staging (including testicular volumes), hand and wrist X-rays, and gonadotrophins assessments (lutenizing hormone and follicle stimulating hormone, testosterone in boys and estradiol in girls).
A briefing document regarding this study and addressed to the FDA is provided as an attachment. In the briefing document the company indicates that while work on the study protocol was initiated in 2003 and first patients visit was planned for November of 2005, the finalization of the protocol required more time than expected due to emerging issues with respect to suicidality in children and adolescents treated with SSRIs and due to the toxicological findings in juvenile rats. The company now

anticipates problems and delays in the recruitment of patients for this study in the face of current discussion regarding the safety of SSRI in children and adolescents and due to the added outcomes measures that were requested by the FDA and MHRA. It is stated that ".. due to the potential for recruitment issues to ultimately prevent study completion, Lilly believes it is unrealistic to expect the final clinical report to be submitted within he requested time frame". It is therefore proposed that the results of a retrospective study (HCLS) on growth and height in juvenile patients, which will become available in May 2005, might provide sufficient answers regarding this issues. However, results of this study are not provided by the company even though according to the briefing document these were planned to be available by the time the response was written.

A previously conducted search of the company's post-marketing adverse event database for events indicating delayed maturation or sexual dysfunction revealed 26 such events in patients younger than 18 during the past 21 years. The results were submitted in April 2004. A report covering a 22-years time period will be included in the next PSUR to be submitted in November 2005.
For the purpose of responding to the current questions, a search covering a 5-year time period (March 2000 - March 2005) was conducted to identify events suggesting growth retardation or delayed sexual maturation. Out of a total of 885 paediatric patients who experience AEs during this period, 81 patients, involving 95 events, experienced events related to growth retardation or delayed sexual maturation. These included:

- 17 cases with weight loss, of which 3 had no confounding factors.
- 25 cases with weight gain of which 12 cases had no confounding factors. Weight gain ranged between 6 and 66 pounds
- 13 cases experienced breast disorder (6 Galactoria with insufficient information for thorough evaluation, 3 gynecomastia of which one had no confounding factors, and other breast disorders)
- 8 cases with growth retardation
- 4 cases with penis disorders (2 priapism 1 erectile dysfunction and one hypospadias in an infant)
- 13 cases of menstrual irregularity
- 2 cases of delayed puberty both exposed concomitantly to methylphenidate.
- 7 cases of other various disorders

It is concluded that the results are inconclusive with respect to the concern regarding the risk of delays in growth and sexual maturation.

Finally, it is noted that the following statement was agreed for inclusion in the fluoxetine SPC following the recent Article 31 referral:

'In addition, long-term safety data in children and adolescents concerning growth, maturation, and cognitive and behavioural development are lacking'.

ASSESSORS COMMENT

The company is requested to inform the CHMP whether there are still plans to carry out study HCLT. Furthermore, a clarification is requested regarding the results of study HCLS and the results of this study should be submitted as soon as possible, as is the special attention to this issue in the next PSUR (to be submitted in November

of 2005).

Results from the post marketing adverse events database are curious in that only 26 events related to delay in growth and sexual maturation were identified in the search of 21-years time period while 95 events were identified in last 5 years. This discrepancy should be explained.

Altogether, little information was provide in this response that could alleviate the concern about delayed growth and sexual maturation.

<u>Question 11:</u> Effects on reproductive organs: The MAH should assess the level of endocrine disruption in the clinical setting. The MAH is asked to compile available clinical data, and, if insufficient further data should be obtained.

COMPANY RESPONSE

The company refers to the response provided to question 10. However, the retrospective study (HCLS) that is described in the response to question 10 focuses on growth but not on specifically on reproductive organs. The search of the company's AE data base to be submitted in the next PSUR will provide information regarding delayed sexual maturation.

ASSESSORS COMMENT

This response indicates that only limited information is likely to become available regarding the concerns about effects on reproductive organs. Hence this concern remains.

<u>Question 12:</u> Request for data on long term safety in children and adolescents was part of a FDA post-authorisation commitment. The MAH should provide the study protocol for review. Furthermore, an update of the status of the clinical trial including information on the discussions with the FDA should also be given.

COMPANY RESPONSE: Refers to response to question 10.

ASSESSORS COMMENT

If study HCLT will not be carried out then evidence concerning long-term safety will remain lacking.

Question 13: ***The suicidality results in TADS indicate an increased risk of suicidality with fluoxetine, which is in line with other SSRIs. In addition to the outcome of the art 31 referral, the suicidality results in TADS should be included in the SPC.***

See also Q4 and Q5 in the non-clinical section, where both non-clinical and clinical data should be addressed.

COMPANY RESPONSE:

Results form the TADS indicate that the combination of fluoxetine with cognitive-behavioural therapy was superior to fluoxetine alone and that patients in all four treatment groups improved significantly on "suicidal thinking". Furthermore it is stressed that no completed suicide occurred in this study.

The company considers the CHMP proposed text for a warning concerning suicidality as appropriate and as based on all fluoxetine data, including the TADS. It is recommended that wording similar to that found in the US label be added to the SPC. This will address the TADS data results.

ASSESSORS COMMENT
The current CHMP text is adequate.