HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE
Opinion
9 July 2014

PROZAC 20 mg, scored dispersible tablets
Box of 28 scored dispersible tablets (CIP: 34009 345 053 1 7)
PROZAC 20 mg, hard capsule
Box of 14 hard capsules (CIP: 34009 331 009 5 7)
PROZAC 20 mg/5 ml, oral solution
Vial of 70 ml with dispensing pipette (CIP: 34009 336 042 0 2)

Applicant: LILLY France

INN	Fluoxetine
ATC code (2013)	N06AB03 (selective serotonin reuptake inhibitors)
Reason for the review	**Renewal of inclusion**
List concerned	**National Health Insurance (French Social Security Code L.162-17)**
Indications concerned	**"Adults:** **• Major depressive episodes (i.e. clear episodes).** **• Obsessive compulsive disorder.** **• Bulimia: as a complement to psychotherapy, indicated for the reduction of binge-eating and vomiting or purging.** ***Children aged 8 years and above and adolescents*:** **• Moderate to severe major depressive episode (i.e. a clear episode), if depression is unresponsive to psychological therapy after 4-6 sessions. Antidepressant medication should be offered to a child or young person with moderate to severe depression only in combination with a concurrent psychological therapy."**

01 ADMINISTRATIVE AND REGULATORY INFORMATION

Marketing Authorisation	16 June 1988 (national procedure) Extension of the indication "bulimia": 25 August 2003 (European harmonisation) Extension of the indication "major depressive episode in children aged 8 years and above": 6 December 2007 (European harmonisation)
Prescribing and dispensing conditions /special status	List I

ATC Classification	2013	
	N	Nervous system
	N06	Psychoanaleptics
	N06A	Antidepressants
	N06AB	Selective serotonin reuptake inhibitors
	N06AB03	fluoxetine

02 BACKGROUND

Examination of the PROZAC proprietary medicinal products reincluded on the list of medicines refundable by National Health Insurance with effect from 29 September 2007 by Order published in the Official Gazette (OJ) of 6 February 2009.

In its previous Opinion (26 September 2007), the Committee's conclusion was as follows: the actual benefit provided by these proprietary medicinal products remains substantial in "major depressive episodes" and "obsessive-compulsive disorders".

The actual benefit provided has not been assessed in the indications "bulimia" and "major depressive disorders in children aged 8 years and above." The company is not applying for the inclusion of PROZAC on the list of medicinal products refundable by National Health Insurance or on the list of medicines approved for hospital use in these indications. There are no other medicines in these last two indications.

03 CHARACTERISTICS OF THE MEDICINAL PRODUCT

03.1 Therapeutic indications

"Adults:
• Major depressive episodes (i.e. clear episodes).
• Obsessive compulsive disorder.
• Bulimia: as a complement to psychotherapy, indicated for the reduction of binge-eating and vomiting or purging.

Children aged 8 years and above and adolescents:
• Moderate to severe major depressive episode (i.e. clear episodes), if depression is unresponsive to psychological therapy after 4-6 sessions. Antidepressant medication should be offered to a child or young person with moderate to severe depression only in combination with a concurrent psychological therapy."

03.2 Dosage

“Major depressive episodes
Adults and the elderly
The recommended dose is 20 mg daily. It should be reviewed and adjusted if necessary, within 3 to 4 weeks of initiation of therapy and thereafter as judged clinically appropriate. Although there may be an increased potential for undesirable effects at higher doses, in some patients, with insufficient response to 20 mg/day, the dose may be increased gradually up to a maximum of 60 mg/day (see section 5.1 of the SPC). Dosage adjustments should be made carefully on an individual patient basis, to maintain the patients at the lowest effective dose.
Patients with depression should be treated for a sufficient period of at least 6 months to ensure that they are free from symptoms.

Obsessive compulsive disorder
Adults and the elderly
The recommended dose is 20 mg daily. Although there may be an increased potential for undesirable effects at higher doses, in some patients, if after two weeks there is insufficient response to 20 mg/day the dose may be increased gradually up to a maximum of 60 mg/day. If no improvement is observed within 10 weeks, treatment with fluoxetine should be reconsidered. If a good therapeutic response has been obtained, treatment can be continued at a dosage adjusted on an individual basis.
While there are no studies to answer the question of how long to continue fluoxetine treatment, obsessive compulsive disorder is a chronic condition and it is reasonable to consider continuation beyond 10 weeks in responding patients.
Dosage adjustments should be made carefully on an individual patient basis, to maintain the treatment at the lowest effective dose. The need for treatment should be reassessed periodically.
Some clinicians advocate concomitant behavioural psychotherapy for patients who have done well on pharmacotherapy.
Long-term efficacy (more than 24 weeks) has not been demonstrated in obsessive compulsive disorder.

Bulimia
Adults and the elderly
A dose of 60 mg/day is recommended.
Long-term efficacy (more than 3 weeks) has not been demonstrated in bulimia.

Adults - all indications
The recommended dose may be increased or decreased. Doses above 80 mg/day have not been assessed.
Fluoxetine can be administered in one or more daily doses, during or between meals.
If treatment is stopped, the active substances persist in the body for several weeks. This should be borne in mind when starting or stopping treatment.
The capsule and dispersible tablet forms are bioequivalent.

Children aged 8 years and above and adolescents – (Moderate to severe major depressive episode)
Treatment should be initiated and monitored under specialist supervision. The starting dose is 10 mg/day, given as 2.5 ml of PROZAC 20 mg/5 ml, oral solution.
Dosage adjustments should be made carefully on an individual patient basis, to maintain the patient at the lowest effective dose.
After one to two weeks of treatment, the dose may be increased to 20 mg/day. Clinical trial experience with daily doses greater than 20 mg/day is very limited. There are only limited data on treatment periods longer than 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).
For paediatric patients who respond to treatment, the need for continued treatment after 6 months should be reviewed. If no clinical benefit is achieved within 9 weeks, treatment should be reconsidered.

Elderly patients:
Caution is recommended when increasing the dose, and the daily dose should generally not exceed 40 mg. However, the maximum recommended dose is 60 mg/day.
A lower or less frequent dose (e.g. 20 mg every second day) should be considered in patients with hepatic impairment (see section 5.2 of the SPC), or in patients where concomitant medication has the potential for interaction with PROZAC (see section 4.5 of the SPC).

Withdrawal symptoms seen on discontinuation of PROZAC:
Abrupt discontinuation of treatment should be avoided. When stopping treatment with PROZAC the dose should be gradually reduced over a period of at least one to two weeks in order to reduce the risk of withdrawal reactions (see sections 4.4 and 4.8 of the SPC). If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, resuming the previously prescribed dose may be considered. Subsequently, the physician may continue decreasing the dose, but at a more gradual rate."

04 ANALYSIS OF NEW AVAILABLE DATA

04.1 Efficacy

04.1.1 Major depressive episodes (i.e. clear episodes)

Since the previous Transparency Committee Opinion of 26 September 2007, two meta-analyses have been found that evaluated the efficacy and safety of fluoxetine in the treatment of major depressive episodes (MDEs) in adults.

- Cipriani et al. in a 2009 Cochrane meta-analysis compared the efficacy and safety of fluoxetine with that of other antidepressants in the treatment of major depressive episodes;[1]
- In 2009 Cipriani A et al. compared the efficacy and acceptability of 12 "new generation" antidepressants (including fluoxetine) in the acute treatment of a major depressive episode;[2]

[1] Cipriani A *et al.* Fluoxetine versus other types of pharmacotherapy for depression. Cochrane Database of Systematic Reviews 2009, Issue 4
[2] Cipriani A. *et al.* Comparative efficacy and acceptability of 12 new-generation antidepressants: a multiple-treatment meta-analysis. The Lancet 2009;373:746-58.

a) Cochrane Review 2009[1]

Methods

Cipriani et al. compared the efficacy and safety of fluoxetine with that of other antidepressants in the treatment of depression in adults. Randomised studies comparing fluoxetine with another antidepressant in the treatment of depression were included.

The efficacy endpoints were the percentage of responders to the acute phase of treatment (6 to 12 weeks) and the change in the score on the Hamilton HAMD depression scale, the Montgomery-Asberg Scale (MADRS) or on another depression assessment scale. Responder patients were patients with a reduction, by comparison with baseline, of at least 50% in the score on the MADRS or on another scale.

Results

A total of 132 randomised studies were included in the meta-analysis. Fluoxetine was compared:

- with tricyclic antidepressants in 58 studies: clomipramine (5), desipramine (3), dothiepin (6), doxepin (4), imipramine (14), lofepramine (1), nomifensine (1), nortriptyline (3), trimipramine (1),
- with heterocyclics in 9 studies: maprotiline (6), mianserin (3),
- with a selective serotonin reuptake inhibitor (SSRI) in 22 studies: citalopram (2), ruvoxamine (1), paroxetine (8), sertraline (9) plus paroxetine and sertraline in the same study (2),
- with other more recent antidepressants (not all of which are marketed in France) in 44 studies: amineptine (2), ABT-200 (1), amisulpride (1), buproprion (1), duloxetine (1), hypericum (3), milnacipran (2), mirtazapine (2), moclobemide (7), nefazodone (3), phenelzine (1), pramipexole (1), reboxetine (2), tianeptine (4), trazodone (3) and venlafaxine (10).

No difference was found between fluoxetine and tricyclics or heterocyclics in the number of responder patients or in the improvement in score on depression assessment scales.
A comparison of SSRIs and more recent antidepressants revealed the following:

- greater efficacy of fluoxetine by comparison with milnacipran in terms of the improvement on depression assessment scales (minimum standard difference [MSD] = -0.38 95% CI [-0.71; -0.,06]);
- no difference by comparison with paroxetine;
- greater efficacy of mirtazapine by comparison with fluoxetine on the number of responder patients (OR = 1.64 95% CI [1.01; 2.65]) but no difference between these 2 medicines as regards the improvement on depression assessment scales; greater efficacy of venlafaxine and sertraline in terms of the number of responder patients (versus venlafaxine OR = 1.40 95% CI [1.15; 1.70]; versus sertraline OR = 1.40 95% CI [1.11; 1.76]) and as regards the improvement on depression assessment scales (versus venlafaxine MSD = 0.11 95% CI [0.00; 0.23]; versus sertraline MSD = 0.22 95% CI [0.00; 0.44])

The authors conclude that significant differences in terms of efficacy and safety are observed between fluoxetine and certain antidepressants, but the clinical significance of these differences is uncertain and no conclusions can be drawn from them for clinical practice. From a clinical point of view, analysis of the safety profile of antidepressants continues to be of great importance, and more data are needed in order to reach a decision. According to the authors, pending these more robust results, treatment decisions should be based on the patient's clinical history, the safety of each product and its acceptability to the subject.

b) Cipriani et al., 2009[2]

Methods

Cipriani et al. compared 12 “new generation” antidepressants (bupropion, citalopram, duloxetine, escitalopram, fluoxetine, fluvoxamine, milnacipran, mirtazapine, paroxetine, reboxetine, sertraline and venlafaxine) in the acute therapy of major depression in adults.
Randomised studies comparing “new generation” antidepressants in the acute therapy (6 to 12 weeks) of major depression were included. Any placebo groups were excluded. A meta-analysis of direct comparison studies and a Bayesian network meta-analysis were performed.
Two criteria were assessed:

- the percentage of responders (efficacy endpoint): patients with a reduction of less than 50% in score on the Hamilton or MADRS depression scales, or patients who were “improved” or “very much improved” on the CGI scale;
- the percentage of premature drop-outs (acceptability endpoint).

Results

A total of 117 randomised studies with a total of 25,928 patients were included. Fifty-eight studies compared fluoxetine with another antidepressant: bupropion (3 studies), citalopram (5 studies), duloxetine (1 study), escitalopram (2 studies), fluvoxamine (2 studies), minalcipran (3 studies), mirtazapine (5 studies), paroxetine (13 studies), reboxetine (4 studies), sertraline (8 studies), venlafaxine (12 studies).

- Results of comparisons with fluoxetine

Fluoxetine was less effective as regards the percentage of responders than mirtazapine (5 studies; 622 patients; OR = 0.65, 95% CI [0.45-0.93]), sertraline (8 studies; 1352 patients; OR = 0.70, 95% CI [0.56-0.88]) and venlafaxine (12 studies; 2446 patients; OR = 0.74, 95% CI [0.62-0.88]).
No difference was seen with the other eight antidepressants with which it was compared (bupropion, citalopram, duloxetine, escitalopram, fluvoxamine, minalcipran, paroxetine, reboxetine).
No difference was found in the percentage of premature drop-outs between fluoxetine and the antidepressants included in the meta-analysis.

- Results of the network meta-analysis

In the Bayesian network meta-analysis, the 12 antidepressants were compared two by two for percentage of responders and percentage of premature drop-outs.
Four antidepressants (mirtazapine, venlafaxine, sertraline and escitalopram) were more effective than five other antidepressants (duloxetine, fluoxetine, fluvoxamine, paroxetine and reboxetine) as regards the percentage of responders. There was no difference in efficacy between escitalopram and citalopram.
Premature drop-outs were numerically less common with escitalopram, sertraline, citalopram and bupropion than with the other antidepressants. However, no significant difference in terms of the percentages of premature drop-outs between fluoxetine and the other antidepressants was observed.

The authors concluded that there were clinically significant differences in terms of efficacy and acceptability between the “new generation” antidepressants in favour of escitalopram and sertraline. Sertraline is, according to them, the best option for starting treatment of moderate to severe depression in adults because of its added value in terms of efficacy and safety.

04.1.2 Bulimia

PROZAC has Marketing Authorisation in the treatment of bulimia as a complement to psychotherapy.
The applicant supplied the results of 2 studies (dating from 1989 and 1996) which evaluated the efficacy of fluoxetine in the management of bulimia. It should be noted that the subjects included were not receiving any psychological therapy. The results of these studies must therefore be used with caution.

Reference	B1Y-MC-HCEQ (Goldstein[3])
Type of study	Phase III, multicentre, randomised, 2-parallel-group, double-blind study versus placebo
Date and duration of study	1989; 16 weeks
Study objective	To compare the efficacy and safety of fluoxetine versus [...] in patients with bulimia
METHOD	
Selection criteria	Patients aged 18 years and over who have had bulimia (diagnosed as per DSM-III R) for at least 6 months, with at least 3 episodes a week of vomiting following excessive food consumption
Study sites	15 centres in the USA
Products studied	Fluoxetine 60 mg/day or placebo for 16 weeks
Primary efficacy endpoints	Efficacy measured as the number of episodes of vomiting and overeating per week. Safety assessed as the percentage of adverse events (AEs)
Selected secondary endpoints	Response to treatment defined as a reduction of 50% in episodes of bulimia a week (vomiting, overeating) between inclusion and the patient's last study visit. A moderate response is defined as a reduction of 50-74%. Assessment of depression on the Hamilton 21-item depression rating scale (HAMD-21) Discontinuation of treatment on account of an adverse event
Randomisation	3 : 1 (fluoxetine : placebo)

[3] Goldstein DJ, Wilson MG, Thompson VL, Potvin JH, Rampey AH Jr. Long-term fluoxetine treatment of bulimia nervosa. Fluoxetine Bulimia Nervosa Research Group. Brit J Psychiatry 1995; 166:660-6

RESULTS	
Number of subjects analysed	398 patients were randomised: 296 were treated with fluoxetine and 102 received placebo.
Patient characteristics and comparability between groups	Most of the patients were Caucasian women, aged between 17 and 63 years. The medians of the number of episodes of vomiting and overeating were similar between the 2 groups. The demographic and clinical characteristics of the two treatment groups were comparable. The mean number of episodes of vomiting on inclusion was 9 episodes a week in the 2 arms of the study (fluoxetine and placebo). The mean number of episodes of overeating on inclusion was 9 episodes a week in the fluoxetine group and 9.5 in the placebo group.
Results for the primary efficacy endpoints	The efficacy of fluoxetine was significantly superior to that of placebo on the reduction: - in the mean number of episodes of vomiting per week -4 versus -2 ($p<0.001$), a reduction of 50% versus 21% - in the number of episodes of overeating per week -4 versus -2 ($p<0.001$), a reduction of 50% versus 18%. As regards safety, the following adverse events were significantly more common with: - fluoxetine: insomnia, nausea, asthenia, anxiety, trembling, dizziness, yawning, sweating, reduced libido; - placebo: depression, myalgia, emotional instability, conjunctivitis. Safety results: See section 4.2 “Safety/adverse effects”
Results for the secondary endpoints	Response to treatment: by comparison with placebo, the results are in favour of fluoxetine: • response (reduction > 50%) to treatment: vomiting: 53.1% versus 35%, p=0.002; overeating: 51.4% versus 36%, p=0.008; • moderate response (reduction of 50-74%) to treatment: vomiting: 15.5% versus 6%, p=0.002; overeating: 16.6% versus 7%, p=0.005. Assessment on the HAMD-21 scale: • On inclusion, the HAMD-21 scores were in the “non-depressive” range in the 2 treatment groups (10 for the fluoxetine group and 8.5 for the placebo group). • At the end of the study, the patients in the 2 treatment groups showed a reduction in the total median score of 5 points, with no statistical difference between the treatment groups. The percentage of drop-outs on account of adverse events was comparable in the 2 treatment groups (fluoxetine 10.8% versus placebo 5.9%, p not significant).

Reference	B1Y-MC-HCIE (Romano[4])
Type of study	Phase IV, multicentre, double-blind, randomised, 2-parallel-group study versus placebo
Date and duration of study	1996; 52 weeks
Study objective	To compare the efficacy and safety of fluoxetine versus placebo in preventing relapses of bulimia during a period of 52 weeks
METHOD	
Selection criteria	Patients aged 18 years and above, suffering from bulimia with episodes of vomiting (diagnosed as per DSM-IV)
Study size and sites	16 centres in the USA
Products studied	Period I: patient selection period, without administration of treatment. Period II: all patients received 60 mg fluoxetine a day (8 weeks) Period III: double-blind phase for the prevention of relapses during which the responder patients from period II were randomised to two groups, fluoxetine 60 mg/day or placebo (52 weeks). The response to treatment is defined as a reduction of at least 50% in the weekly number of episodes of vomiting.
Primary efficacy endpoints	Time until relapse of bulimia during the 52-week period III (period between randomisation and the time when the patient has a "relapse") Rate of relapse determined by the number of episodes of vomiting a week. Patients were regarded as having a "relapse" during the double-blind treatment phase if they showed, for 2 consecutive weeks, the same frequency of vomiting per week as on inclusion.
Selected secondary endpoints	Change in the number of episodes of overeating Change in the number of episodes of vomiting
Randomisation	1 : 1

[4] Romano SJ, Halmi KA, Sarkar NP, Koke SC, Lee JS. A placebo-controlled study of fluoxetine in continued treatment of bulimia nervosa after successful acute fluoxetine treatment. Am J Psychiatry 2002;159:96-102

RESULTS	
Number of subjects analysed	Period II: 232 patients were included in the 8-week phase of acute treatment with fluoxetine Period III: 150 patients were randomised during the double-blind relapse prevention phase: 76 patients to the fluoxetine group and 74 to the placebo group.
Patient characteristics and comparability between groups	98% of the patients randomised were women; 90.7% were Caucasian. The mean age was 29.8 years The demographic and clinical characteristics of the two treatment groups were comparable.
Primary efficacy endpoint results	Time to relapse: according to the Kaplan-Meier curves, the time to relapse was statistically significantly longer in the fluoxetine group than in the placebo group (p=0.008). Relapse rate: No significant difference was found between the two treatment groups: 33% for fluoxetine versus 51% for placebo.
Secondary endpoint results	During phase III, an increase was seen in the mean number of episodes of overeating which was significantly larger in the placebo group than in the fluoxetine group (4.1 versus 2.5, p=0.03). During this period, the increase in the mean number of episodes of vomiting was significantly larger in the placebo group than in the fluoxetine group (4.8 versus 2.9, p=0.021).

Conclusion of the 2 studies:
The first study (Goldstein) evaluated the efficacy of fluoxetine versus placebo, over 16 weeks, in bulimic patients. The results showed a significant reduction in favour of fluoxetine of about 50% by comparison with placebo (about 20%) in terms of the number of episodes of vomiting a week and in the number of episodes of overeating.

The second study (Romano) evaluated the efficacy of fluoxetine versus placebo in preventing relapses of bulimia during a period of 52 weeks. This study was performed only in responder patients after 8 weeks of treatment with fluoxetine. These patients do not correspond to the population defined by the wording of the indication in the Marketing Authorisation. The results are therefore exploratory. There was shown to be an improvement in the time to relapse in the fluoxetine group by comparison with the placebo group but no difference in the relapse rate between the 2 treatment groups.

In addition, it must be pointed out that no psychological therapy was given to subjects included in each of the 2 studies.

04.1.3 Major depressive episode in children aged 8 years or above with no response to psychological therapy

The Marketing Authorisation states that PROZAC is indicated if the patient is unresponsive to psychotherapy after 4-6 sessions and that antidepressant treatment should be offered to a child or adolescent suffering from moderate to severe depression only in combination with concomitant psychotherapy. The starting dose is 10 mg/day. After one to two weeks of treatment, the dose can be increased to 20 mg/day.

The applicant supplied the results of 3 studies evaluating fluoxetine versus placebo (including one study which also evaluated the combination of fluoxetine and cognitive behavioural therapy). These data cannot be taken into account because they are outside the scope of the, and their clinical relevance is debatable: none of the studies was performed if there was no response at the end of psychological therapy;

- If there is no clinical improvement after 9 weeks, treatment with PROZAC must be reconsidered, according to the Marketing Authorisation. However, these studies do not specify whether this evaluation at the start of treatment was performed in the children included;
- During study B1Y-MC-X05,[5] no change in dose was made at the start or end of treatment; also, the period of treatment was limited to 8 weeks;
- During study B1Y-MC-HCJE,[6] after a phase during which the dosage was 10 mg/day, treatment was 20 mg/day for 9 weeks. After this 20 mg/day phase, non-responding patients were treated for 10 weeks with an increased dosage (40-60 mg/day) which was higher than the one recommended in the SPC. In addition, there are question marks about the relevance of prescribing fluoxetine to all non-responding patients after 9 weeks and of increasing the dosage;
- The TADS study[7] compared 4 treatment groups in subjects aged 12-17 years: fluoxetine, fluoxetine + cognitive behavioural therapy, cognitive behavioural therapy, placebo, without adjustment for multiple comparisons. And the dosages ranged from 10 to 40 mg/day.

With these limitations, the results of these studies are presented for information purposes.

a. Emslie study 1991

Reference	B1Y-MC-X065 (Emslie 1991)[4]
Type of study	Randomised, single-centre, parallel-group, double-blind, placebo-controlled.
Date and duration of study	1991; 8 weeks
Study objectives	To compare the efficacy and safety of fluoxetine 20 mg/day versus placebo for the treatment of MDEs in children and adolescents
METHOD	
Inclusion criteria	Patients aged 8 to 18 years with moderate to severe MDE (DSM-III R classification)
Products studied	Fluoxetine 20 mg/day for 8 weeks or placebo
Primary efficacy endpoint	Response rate, defined as a reduction ≥30% in the total Children's Depression Rating Scale-Revised score (CDRS-R), measured at the end of the study.
Secondary endpoint	Improvement in the Clinician Global Impression (CGI) score, measured at the end of the study.

[5] Emslie GJ, Rush AJ, Weinberg WA, Kowatch RA, Hughes CW, Carmody T, Rintelmann J. A double-blind, randomized, placebo-controlled trial of fluoxetine in children and adolescents with depression. Arch Gen Psychiatry 1997;54:1031-7

[6] Emslie GJ, Heiligenstein JH, Wagner KD, Hoog SL, Ernest DE, Brown E, Nilsson M, Jacobson JG. Fluoxetine for acute treatment of depression in children and adolescents: a placebo-controlled, randomized clinical trial. J Am Acad Child Adolesc Psychiatry 2002;41:1205-15

[7] March J, Silva S, Petrycki S, Curry J, Wells K, Fairbank J, Burns B, Domino M, McNulty S, Vitiello B, Severe J. Treatment for Adolescents With Depression Study (TADS) Team. Fluoxetine, cognitive-behavioral therapy, and their combination for adolescents with depression: Treatment for Adolescents With Depression Study (TADS) randomized controlled trial. JAMA 2004;18; 292: 807-20

RESULTS	
Number of subjects analysed	96 (48 in each group)
Follow-up period	8 weeks
Patient characteristics and comparability between groups	Patients mostly Caucasian (79%), mean age 12.8 years. The demographic and clinical characteristics of the two treatment groups were comparable.
Results for the primary endpoint	The patient responder rate was significantly higher in the fluoxetine group (58%) than in the placebo group (32%), p=0.013.
Results for the secondary endpoint	The improvement in the CGI score was significantly greater in the fluoxetine group (mean improvement in score = 2.5) than in the placebo group (mean improvement in score = 3.2), p=0.015. (An improvement in the CGI score of 2 corresponds to a marked improvement, and an improvement of 3 corresponds to a moderate improvement).

Conclusion of the study:
Performed outside the indication of the Marketing Authorisation, the Emslie 1991 study showed a significant difference in favour of fluoxetine by comparison with placebo in children aged 8 to 18 years with a moderate to severe MDE in terms of responder patients during a limited treatment period (8 weeks).

b. Emslie study 1998

Reference	B1Y-MC-X065 (Emslie 1998)[5]
Type of study	Multicentre, double-blind, randomised, parallel-group placebo-controlled study consisting of 5 phases: - phase I: selection period (2 weeks); - phase II: washout period (1 week): single-blind administration of placebo; - phase III: adjustment period (1 week): randomisation to 2 groups (placebo and fluoxetine 10 mg/day). At the end of this week, patients in the fluoxetine group who had not tolerated the treatment were excluded from the study. - phase IV: treatment for 9 weeks (fluoxetine 20 mg/day or placebo) - phase V: continuation of treatment for 10 weeks in non-responders (fluoxetine 40 or 60 mg/day)
Date and duration of study	1998; 28 weeks
Study objectives	Phase IV: to compare the efficacy and safety of fluoxetine 20 mg/day with placebo in the acute treatment (up to 9 weeks) of MDEs in children and adolescents Phase V: to compare the efficacy and safety of fluoxetine 20 mg/day and fluoxetine 40 or 60 mg/day for the treatment of MDEs in children and adolescents who did not respond to treatment with fluoxetine 20 mg/day (up to 10 weeks of treatment)
METHOD	
Inclusion criteria	Patients aged 8 to 18 years with moderate to severe major depressive episode (MDE) (as per DSM-III R)
Products studied	Phase III (adjustment period, 1 week): fluoxetine 10 mg/day or placebo. Phase IV (acute treatment phase of 9 weeks): fluoxetine 20 mg/day or placebo. Phase V (for patients who did not respond to phase III, 10 weeks of treatment): fluoxetine 20 mg/day or 40–60 mg/day.
Primary efficacy endpoint	Responder rate, defined as a reduction ≥ 30% in the total CDRS-R score measured at the end of phase IV
Selected secondary endpoints	Change in the CDRS-R score at the end of phase IV Change in the CDRS-R score at the end of phase V

RESULTS	
Number of subjects analysed	219 (fluoxetine n=109, placebo n=110)
Follow-up period	19 weeks: - Phase IV acute treatment phase (9 weeks): - Phase V of treatment for nonresponder patients (10 weeks)
Patient characteristics and comparability between groups	Patients mostly Caucasian (82%), mean age 12.7 years. The demographic and clinical characteristics of the two treatment groups were comparable.
Results for the primary efficacy endpoint	No statistically significant difference was seen between the response rates for the two groups (response rate for fluoxetine = 65%, response rate for placebo = 54%, p not significant) at the end of phase IV.
Results for the secondary endpoint	At the end of phase IV, fluoxetine was statistically superior to placebo in the reduction in the CDRS-R score: -22 for fluoxetine, -15 for placebo, p<0.001. At the end of phase V, no statistically significant difference was seen in the reduction in the CDRS-R score (-9.4 in the fluoxetine 40 or 60 mg/day group and -1.5 for fluoxetine 20 mg/day)

Conclusion of the study:
Also outside the indication of the Marketing Authorisation, the Emslie 1998 study did not show any significant difference between fluoxetine and placebo in the same primary efficacy endpoint as the previous study in a similar population of patients aged 8 to 18 years with moderate to severe MDE (DSM-III R classification) for a treatment period of 9 weeks (plus one week at 10 mg/day at the start of treatment).

c. TADS study[8] (Treatment for Adolescents with Depression Study)

Reference	TADS
Type of study	Multicentre, randomised, controlled, parallel-group study
Date and duration of study	2000; 12 weeks
Study objective	To evaluate the efficacy of 4 treatments in adolescents with major depressive episodes
METHOD	
Inclusion criteria	Patients aged 12 to 17 years with moderate to severe MDE (according to DSM-IV)
Products studied	For 12 weeks, patients received, according to their treatment group: 1- Fluoxetine (10-40 mg/day) 2- Cognitive behavioural therapy (CBT) 3- CBT + fluoxetine (10-40 mg/day) 4- Placebo The placebo and fluoxetine were administered double-blind.
Primary efficacy endpoints	Change in the total CDRS-R score Positive response rate defined as an improvement in the CGI score of 1 (very substantial improvement) or 2 (substantial improvement)
Secondary endpoint	RADS Scale (Reynolds Adolescent Depression Scale)

RESULTS

[8] March J, Silva S, Petrycki S, Curry J, Wells K, Fairbank J, Burns B, Domino M, McNulty S, Vitiello B, Severe J; Treatment for Adolescents With Depression Study (TADS) Team. Fluoxetine, cognitive-behavioral therapy, and their combination for adolescents with depression: Treatment for Adolescents with Depression Study (TADS) randomized controlled trial. JAMA 2004;18;292:807-20

Number of subjects analysed	439 (fluoxetine n=109, CBT + fluoxetine n=107, CBT n=111, placebo n=112)
Date and duration of study	2000; 12 weeks
Patient characteristics and comparability between groups	Mean age 14.6 years The demographic and clinical characteristics of the four treatment groups were comparable.
Results for the primary efficacy endpoints	The results below must be used with caution because not adjustment has been made for the multiplicity of tests. CDRS-R The changes in CDRS-R were as follows: Fluoxetine + CBT: -27.00 Fluoxetine alone: -22.64 CBT alone: -23.34 Placebo: -19,41 The combination fluoxetine + CBT was superior to fluoxetine alone (p=0.02), to CBT alone (p=0.01) and to placebo (p=0.001). Fluoxetine alone (p=0.10) and CBT alone (p=0.40) showed no difference by comparison with placebo. Fluoxetine alone was more effective than CBT alone (p=0.01). Positive response rate: Fluoxetine: 71.0% Fluoxetine + CBT: 60.6% CBT: 46.2% Placebo: 34.8% The patient responder rates were higher for the groups fluoxetine alone or fluoxetine + CBT by comparison with the responder rates for the CBT or placebo groups (p values not available). No significant difference was found between the groups fluoxetine alone and fluoxetine + CBT (p=0.20)
Secondary endpoint results	The improvement measured on the RADS scale was greater for the combination fluoxetine + CBT by comparison with placebo (p=0.001), whereas that was not the case with fluoxetine alone (p=0.34) or CBT alone (p=0.21). The combination fluoxetine + CBT was superior to fluoxetine alone (p=0.002) and to CBT alone (p=0.001).

Conclusion of the study:
Since they are outside the scope of the Marketing Authorisation and multiple tests, the results for the combination fluoxetine + CBT differ in the 2 primary endpoints: the results are in favour of the combination fluoxetine + CBT compared with fluoxetine alone on the CDRS-R scale and no difference was seen in the positive response rate between fluoxetine + CBT and fluoxetine alone.
In addition, no significant difference was found between the fluoxetine and placebo groups.

Conclusion of the 3 studies:
These studies evaluated the efficacy of fluoxetine outside the scope of the Marketing Authorisation. None of these data allow any effect size to be defined for fluoxetine in the management of moderate to severe major depressive episodes in children (age > 8 years) or adolescents within the indication or at the dosages recommended by the Marketing Authorisation.
In addition, the studies performed evaluated the effect of fluoxetine during periods that were too short for this type of disorder in the course of which patients need to be treated for a period of at least 6 months.

04.1.4 Obsessive compulsive disorders

No new data have been supplied by the applicant in this indication.

04.2 Safety/Adverse effects

Pharmacovigilance
The applicant supplied data from the latest periodic safety update reports (PSURs) covering the period from 8 September 2006 to 7 September 2012. In particular, the "undesirable effects" and "special precautions for use" sections in the SPC have been amended (see annex).
The "adverse effects" section now mentions a risk of prolongation of the QTc and rare cases of torsades de pointes.

Bulimia
In study B1Y-MC-HCEQ, the following adverse events were significantly more common with:
- fluoxetine: insomnia (34.5% versus 18.6%), nausea (30.4% versus 12.7%), asthenia (21.3% versus 6.9%), anxiety (17.6% versus 8.8%), trembling (14.2% versus 2.0%), dizziness (12.5 versus 3.9%), yawning (12.2% versus 0%), sweating (9.5% versus 2.0%), reduced libido (6.4% versus 1.0%);
- placebo: depression (10.1% versus 18.6%), myalgia (4.7% versus 11.8%), emotional instability (2.7% versus 7.8%), conjunctivitis (0.3% versus 2.9%).

Drop-outs linked to adverse effects were 10.8% (n=32) in the fluoxetine group and 5.9% (n=6) in the placebo group.

In study B1Y-MC-HCIE, during the double-blind relapse prevention phase (60 mg/day):
- 117 patients (78%) out of the 150 included in this phase had at least one adverse event (AE) linked to treatment and a greater number of patients treated with fluoxetine than with placebo reported at least one AE (86.8% versus 68.9% in the placebo arm, p=0.010),
- The commonest AEs (≥ 10%) reported with fluoxetine were: rhinitis (31.6%), headaches (19.7%), depression (17.1%), flu-like syndrome (15.8%), insomnia (13.2%), asthenia (11.8%), anxiety (10.5%) and accidental injury (10.5%).
- The commonest AEs (≥ 10%) reported in the placebo arm were: headaches (27%), depression (23%), rhinitis (16.2%) and asthenia (14.9%).

The percentage of patients who prematurely ended the study for any reason was comparable in the 2 treatment arms: 86% (63) for fluoxetine and 92% (68) for placebo.

Children - Major depressive episodes
<u>Adverse effects in clinical studies</u>
In the 2 Emslie studies, two types of AE were identified: solicited AEs (collected by means of a questionnaire) and unsolicited AEs (i.e. reported spontaneously by the patient).

- In study B1Y-MC-X065 (Emslie 1991) lasting 8 weeks, the percentage of patients showing a solicited adverse event was higher in the fluoxetine group (97.9%) than in the placebo group (93.8%). The same is true of unsolicited AEs (95.8% versus 81.3%).

The most commonly observed solicited AEs were: common cold (45.8% in the 2 groups), drowsiness (35.4% with fluoxetine, 31.3% with placebo), diarrhoea (33.3% with fluoxetine, 18.8% with placebo) and cramps (31.3% with fluoxetine, 20.8% with placebo).
The most commonly observed unsolicited AEs were: anxiety (37.5% with fluoxetine, 35.4% with placebo), pharyngitis (25.0% with fluoxetine, 14.6% with placebo), depression (18.8% with fluoxetine, 16.7% with placebo) and vomiting (14.6% with fluoxetine, 4.2% with placebo).

The percentage of premature drop-outs for all causes was 29% (n=14) in the fluoxetine group and 46% (n=22) in the placebo group. The commonest cause of drop-outs was the absence of response to treatment (19 patients who received placebo and 7 patients who received fluoxetine). Stopping the study on account of an adverse effect was [reported by] 4 patients treated with

fluoxetine (3 patients who developed manic symptoms and a rash) and 1 patient who received placebo.

- In the acute treatment phase of study B1Y-MC-HCJE (Emslie 1998), a comparable percentage of patients treated with fluoxetine or placebo had a solicited AE (96% versus 91%) during the acute treatment phase. A total of 98% of patients treated with fluoxetine and 92% of patients in the placebo group had at least one solicited AE during the following treatment phase. During the 2 treatment phases, there was no significant difference between the treatment groups in terms of the incidence of solicited AEs.
As regards unsolicited AEs, 86% of patients treated with fluoxetine reported at least one unsolicited AE, as did 73% of patients in the placebo group (p=0.019) during the acute treatment phase. And during the following phase, 93% of patients treated with fluoxetine and 79% of patients in the placebo group had at least one unsolicited AE. During the acute treatment phase and the following phase, the only unsolicited AEs that occurred more commonly with fluoxetine were headaches (30% versus 16%)
The percentages of premature drop-outs were 17% in the fluoxetine group and 38% in the placebo group.

- In the TADS study, during the 12 weeks of treatment, more AEs were reported in the fluoxetine group than in the fluoxetine + CBT group or in the placebo group. The main AEs were: headaches, insomnia, sedation, vomiting and abdominal pain.
Headaches, the commonest AE, were reported more commonly in the fluoxetine treatment group (11.9%) than in the fluoxetine + CBT group (6.8%) or in the placebo group (10.7%).
The percentages of AEs of a psychiatric nature (including manifestations of mania, irritation, agitation and anxiety) were 11% for the group on fluoxetine alone, 5.6% for the combination fluoxetine + CBT, and 4.5% for the placebo group.
The percentages of premature drop-outs from treatment were 17% in the fluoxetine group, 14% in the fluoxetine + CBT group, 22% in the CBT group and 21% in the placebo group.

<u>ANSM data</u>
When Marketing Authorisation was granted in the treatment of major depressive episodes (i.e. clear episodes) of moderate to severe intensity, in combination with psychological therapy, in children aged 8 years and above or who have not responded to 4-6 sessions of psychotherapy alone, the EMEA asked Lilly to undertake additional studies on the safety profile of PROZAC. This request follows on from the results of a preclinical study in juvenile rats showing deleterious effects of fluoxetine on growth, sexual maturation, sexual function and on the sex organs, particularly irreversible testicular damage.
Because of concerns linked to the safety profile of fluoxetine used to treat children and adolescents, the French Healthcare Product Safety Agency (AFSSAPS) set up a national monitoring system focusing on sexual development and growth.
Two other antidepressants (fluvoxamine and sertraline) indicated in obsessive compulsive disorders in children were included in this follow-up.
A national risk management plan was set up, comprising reinforced national pharmacovigilance follow-up, which has been run under the responsibility of the Bordeaux Regional Pharmacovigilance Centre (CRPV) since February 2008, and a retrospective cohort study which started in June 2010, the main aim of which was to evaluate, in prepubescent boys exposed to SSRIs, pubertal development, sexual maturation and gonad function.

The findings of the Pharmacovigilance Technical Committee (meeting of 14 October 2013) are as follows: in France, the number of reports in the French National Pharmacovigilance database (BNPV) was, respectively, 39, 24 and 79 for fluoxetine, fluvoxamine and sertraline. No adverse effect on growth or sexual maturity was found.
In addition, the retrospective cohort study initially planned in France with the aim of evaluating, in prepubescent boys exposed to SSRIs, pubertal development, sexual maturation and gonad function, has not been carried out. The study was stopped at the end of 2012 because of inclusion

difficulties: 7 patients out of the 100 planned had been included by the time of the report of March 2012.
In conclusion, the national pharmacovigilance follow-up of fluoxetine, fluvoxamine and sertraline in children and adolescents was therefore stopped.

04.3 Usage/prescription data

According to the IMS-EPPM data (moving annual total, autumn 2013), 991,000 prescriptions were written for PROZAC: 520,000 prescriptions for the capsule form, 447,000 prescriptions for the tablet form and 24,000 prescriptions for the oral solution form.
PROZAC capsules are 58% prescribed in “depressive episodes”, 9% in “mixed anxiety and depressive disorders” and 3% in “obsessive compulsive disorders”.
PROZAC tablets are 58% prescribed in “depressive episodes”, 9% in “mixed anxiety and depressive disorders” and 3% in “obsessive compulsive disorders”.
The mean dosage of the tablet form and the capsule form is about 1.2-1.3 units a day.
In 49% of cases these proprietary medicinal products are coprescribed with tranquillisers and in 20% of cases with non-barbiturate hypnotics.

04.4 Therapeutic use

Adults - Major depressive episodes (i.e. clear episodes)
Antidepressants are the standard drug therapy for moderate to severe major depressive episodes.
According to the 2006 guidelines of the National Medicines and Health Products Safety Agency (ANSM, formerly AFSSAPS) 2006, with moderate to severe depressive episodes managed in an outpatient setting, it is recommended that an SSRI (the class that includes fluoxetine), an SNRI or one of the "other antidepressant" class drugs should, because of their better safety, be prescribed as first-line therapy. Within these three classes of product, no one antidepressant is recommended more strongly than the others
NICE recommends a generic SSRI as first-line therapy, and does not recommend one SSRI rather than any other.[9]
Drug therapy is only one aspect of the management of subjects with depressive disorders, and should be considered only in conjunction with psychotherapy. Antidepressants are not indicated in depressive syndromes that do not satisfy the criteria for a major depressive episode.
Fluoxetine remains a first-line option for treating moderate to severe major depressive episodes.

Children - Major depressive episodes (i.e. clear episodes)[10]
In children, the first-line treatment must be psychological. There are no good quality data confirming the value of drug treatment.

In adolescents, the first-line treatment is in most cases psychological.

According to expert opinion, the prescription of fluoxetine can be considered in adolescents from age 15 years onwards with a well-established diagnosis of "clear" depressive episodes, of moderate to severe intensity, as second-line treatment after the failure of at least 8 sessions of psychotherapy. Adolescents receiving drug treatment must be kept under close surveillance.

Prescribing methods
Drug treatment with antidepressants in an adolescent must not be used as a replacement for psychotherapy, which is the first-line treatment. It must be accompanied by close monitoring and checks for suicidal behaviour, particularly at the start of treatment. The choice of antidepressant must take account of the safety profile of each medicinal product.
As in adults, the total duration of treatment for an episode could be between 6 months and one year.

Prevention of recurrences
Recurrence of the depressive disorder must be prevented. An increased frequency of recurrences is a sign of a risk of an unfavourable prognosis. Suitable psychological therapy is the key to preventing recurrences. In addition, advice given to the patient and his/her caregivers, in particular to consult his/her doctor quickly in the event of a change in mood, is needed in order to detect the onset of a relapse at an early stage.

Discontinuation of treatment
Discontinuing an antidepressant must not be done on the initiative of the patient or his/her family without the support of the doctor. Discontinuation of treatment should always be done gradually over several weeks or months to prevent the risk of a recurrence. It should be arranged with the patient and his/her family.

Patient follow-up

[9] NICE Clinical Guideline 90: Depression in adults (update), Full Guideline. 2010. www.nice.org.uk.
[10] The correct use of antidepressants in children and adolescents. Afssaps. January 2008

Active checks of the risk of suicide should be made throughout treatment, whatever form of management is used and particularly if antidepressant treatment is initiated.
Where antidepressant treatment is not warranted from the outset, it is recommended to reassess the situation at regular intervals. If the initiation of antidepressant treatment is necessary, it is very important to put in place close monitoring of the patient (particularly during the first few weeks) and to reassess the treatment regularly. It is necessary to check, with the help of the patient's caregivers, for any sign of hostile behaviour (aggression, oppositional defiant behaviour, anger) or suicidal behaviour (suicidal thoughts and/or threats to commit suicide, suicide attempts), particularly at the start of treatment.
The recent appearance (or worsening) of symptoms such as insomnia, irritability, anxiety, agitation, nervousness and in particular, suicidal thoughts necessitates more frequent consultations.
Effective doctor/family communication facilitates effective treatment of the patient.

Withdrawal syndrome
As in adults, severe symptoms may appear if antidepressant treatment is discontinued too quickly, such as irritability, anxiety, dizziness or sleep disorders.
Prolonged treatment, a high dosage and abrupt discontinuation of the antidepressant are risk factors for the occurrence of withdrawal syndrome. This syndrome occurs in the days after the discontinuation of treatment and can last a week on average.
It is important to follow, and to get the patient and his/her caregivers to follow, the rules for discontinuing treatment, consisting in gradually reducing the dosage so as to reduce the risks of these symptoms appearing.
If withdrawal syndrome occurs, it is important to reassure the patient that the symptoms are transient in nature, and to temporarily return to the previous dosage of the antidepressant if necessary before resuming withdrawal at an even more gradual rate.

Obsessive compulsive disorders[11,12]
In most anxiety disorders, different treatments have proved effective: psychotherapies, particularly cognitive behavioural psychotherapies, antidepressants and a combination of these two treatment types.
Fluoxetine is an alternative medication to antidepressants with Marketing Authorisation in the treatment of obsessive compulsive disorders: clomipramine, escitalopram, fluvoxamine, paroxetine and sertraline.
SSRIs are recommended as a first-line treatment. Clomipramine is recommended as second-line treatment, for safety reasons.
Compared with depressive disorders, the effective dosages in the treatment of OCD may be higher. The duration of action of antidepressants is longer (of the order of 4-8 weeks) than that observed with depressive disorders. Similarly, the period of treatment needed to obtain the maximum response to treatment is longer (10-12 weeks). Thus, treatment must be continued for at least 3 months before it is possible to conclude that it is ineffective. The duration of treatment must be sufficiently long, often longer than one year. It is longer if the disorder is chronic and if there are relapses when treatment is stopped.

Bulimia
Bulimia is an eating disorder which must be treated as soon as possible. Treatment is based mainly on psychological therapy and nutritional education.
With eating disorders, cognitive and behavioural psychotherapies are often used. Their aim is to change the patient's overall attitude to food. In the case of bulimia, they can be used to identify the

[11] Bon usage des médicaments antidépresseurs dans le traitement des troubles dépressifs et des troubles anxieux de l'adulte [The correct use of antidepressant medicines in the treatment of depressive disorders and anxiety disorders in adults]. Afssaps. Recommandations [Guidelines], October 2006.
[12] Troubles obsessionnels compulsifs (TOC) résistants: prise en charge et place de la neurochirurgie fonctionnelle [Refractory obsessive compulsive disorders: management and role of functional neurosurgery]. HAS May 2005.

factors that trigger crises and to learn to adopt behaviour other than feeding frenzy. Advice is given gradually; it includes eating slowly, having regular mealtimes or resisting temptations.
These treatments are almost always combined with nutritional education measures which are intended to change the patient's beliefs about food and about the link between food and weight gain.
Fluoxetine is the only antidepressant with Marketing Authorisation in this indication.

According to expert opinion, fluoxetine could be prescribed when initiating psychotherapy but must not be used for prolonged periods.

05 TRANSPARENCY COMMITTEE CONCLUSIONS

In view of all the above information, and following the debate and vote, the Committee's opinion is as follows:

- **in major depressive episodes and obsessive compulsive disorders the conclusions of its earlier Opinion of 26 September 2007 have not changed.**
- **in the indications bulimia in adults and depression in children, the Committee's Opinion is given below.[13]**

05.1 Actual Benefit:

Adults: Major depressive episodes (i.e. clear episodes).

◗ Major depressive episodes are characterised by depressed mood or a loss of interest or pleasure in almost all activities. The level of functional impairment associated with major depressive episodes varies, but even in mild cases there is distress and/or impairment of social or working life. The most serious consequences of a major depressive episode are attempted suicide or suicide.
◗ Like other SSRIs, fluoxetine is a first-line symptomatic therapy for major depressive episodes.
◗ The efficacy/adverse effects ratio of fluoxetine is substantial.
◗ Alternative drug therapies are the other antidepressants indicated for the treatment of major depressive episodes.

Taking account of these points, the Committee considers that the actual benefit of PROZAC remains substantial in major depressive episodes (i.e. clear episodes) in adults.

Adults: Obsessive compulsive disorder

◗ Obsessive compulsive disorder is characterised by recurrent obsessions or compulsions that are sufficiently severe as to interfere significantly with the subject's normal activities, working life and social life.
◗ Fluoxetine is a symptomatic therapy for obsessive compulsive disorder.
◗ The efficacy/adverse effects ratio of fluoxetine is substantial.
Alternative drug therapies are the other antidepressants indicated for the treatment of obsessive compulsive disorder.
◗ This is a first-line therapy in this indication.

Taking account of these points, the Committee considers that the actual benefit of PROZAC remains substantial in obsessive compulsive disorders.

"Adults: Bulimia, as a complement to psychotherapy

◗ Bulimia is an eating disorder which can have serious consequences and leads to a marked deterioration in quality of life.
◗ Fluoxetine is a symptomatic treatment for bulimia.
◗ In the absence of any robust data that can be used define precisely the size of fluoxetine's effect in this indication, the efficacy/adverse effects ratio of fluoxetine is poorly established in this indication.
◗ The treatment of bulimia is psychotherapy. No other medicines are indicated in bulimia. According to expert opinion, drug treatment can be considered only at the start of treatment, but not in the long term.

[13] In these 2 indications, the applicant has not requested inclusion on the list of refundable medicines and has therefore not claimed any actual benefit.

Taking account of these points, the Committee considers that, in the treatment of bulimia as a complement to psychotherapy, the actual benefit of PROZAC is insufficient.

Children: Moderate to severe major depressive episodes (i.e. clear episodes), if depression is unresponsive to psychological therapy after 4-6 sessions.

- Childhood depression is accompanied by behavioural and relational, family and educational problems that are intractable and often appear suddenly. It usually takes the form of a generally withdrawn attitude or, alternatively, irritability and unusual agitation.
Depression in adolescents make take the form of sudden loss of interest in school, physical complaints masking depression in girls, or criminal acts (aggression or antisocial acts) in boys.
These disorders are distinct from the "adolescent crisis" and the risk of underestimating them is substantial.
- Fluoxetine is intended as symptomatic treatment.
- In the absence of any robust data that can be used to define precisely an effect size of fluoxetine in this indication, the efficacy/adverse effects ratio of fluoxetine is poorly established in this indication.
- Fluoxetine is the only antidepressant with in the treatment of depression in patients under 18 years of age.
- The first-line treatment for depression in children and adolescents is psychotherapy. According to expert opinion, drug treatment can be considered only in adolescents over 15 years of age and only in combination with psychotherapy and accompanied by close monitoring of the patient.

Taking account of these points, the Committee considers that the actual benefit of PROZAC is insufficient in children aged 8 years and over in moderate to severe major depressive episodes (i.e. clear episodes) if these are unresponsive to psychological therapy after 4-6 sessions.

05.2 Transparency Committee recommendations:

The Committee recommends continued inclusion on the list of medicines refundable by National Health Insurance in the indications "major depressive episodes" in adults and "obsessive compulsive disorders" at the dosages in the Marketing Authorisation.

- **Proposed reimbursement rate: 65%**

- **Packaging:** Appropriate for the prescription conditions.

ANNEX		
SPC headings	**Old version**	**New version**
4.1 Therapeutic indications	Treatment of major depressive episodes (i.e. clear episodes). Obsessive compulsive disorder. Bulimia: as a complement to psychotherapy, indicated for the reduction of binge-eating and vomiting or purging.	**Adults** Treatment of major depressive episodes (i.e. clear episodes). Obsessive compulsive disorder. Bulimia: as a complement to psychotherapy, indicated for the reduction of binge-eating and vomiting or purging. **Children and adolescents aged 8 years and above** Moderate to severe major depressive episodes (i.e. clear episodes), if depression is unresponsive to psychological therapy after 4-6 sessions. Antidepressant medication should be offered to a child or adolescent with moderate to severe depression only in combination with a concurrent psychological therapy.
4.2 Posology and method of administration	Oral administration in adults only. **Major depressive episodes** Adults and the elderly: 20-60 mg/day. The recommended starting dose is 20 mg/day. Although there is a risk of an increase in adverse affects with doses over 20 mg/day, an increase in dosage may be considered if there is no response after three weeks of treatment. According to the consensus of the World Health Organisation (WHO), antidepressant treatment can be continued for at least 6 months. **Obsessive compulsive disorder** Adults and the elderly: 20-60 mg/day. The recommended starting dose is 20 mg/day. Although there is a risk of an increase in adverse affects with doses over 20 mg/day, an increase in dosage can be considered if there is no response after two weeks of treatment. If no improvement is observed within 10 weeks, treatment with fluoxetine should be reconsidered. If a good therapeutic response has been obtained, treatment can be continued at a dosage adjusted on an individual basis. While there are no tudies to answer the question of how long to continue fluoxetine treatment, OCD is a chronic condition and it is reasonable to consider continuation beyond 10 weeks in responding patients. Dosage adjustments should be made carefully on an individual patient basis, to maintain the patient at the lowest effective dose. The need for treatment should be reassessed periodically. Some clinicians advocate concomitant behavioural psychotherapy for	Oral administration. ~~in adults only~~ **Major depressive episodes** *Adults and the elderly* ~~Adults and the elderly: 20-60 mg/day.~~ The recommended ~~starting~~ dose is 20 mg/day. It should be reviewed and adjusted if necessary, within 3 to 4 weeks of initiation of therapy and thereafter as judged clinically appropriate. Although ~~there is a risk of an increase in adverse effects at doses greater than 20 mg/day, an increase in dosage can be considered if there is no response after three weeks of treatment~~ the risk of adverse effects increases with the dose, the dosage may be increased gradually in some patients with an inadequate response to the dosage of 20 mg/day, up to a maximum of 60 mg/day (see section 5.1). Dosage adjustments should be made carefully on an individual patient basis, to maintain the patients at the lowest effective dose. ~~According to the consensus of the World Health Organization (WHO), antidepressant treatment can be continued for at least 6 months.~~ Patients with depression should be treated for a sufficient period of at least 6 months to ensure that they are free from symptoms. **Obsessive compulsive disorder** *Adults and the elderly* ~~Adults and the elderly: 20-60 mg/day.~~ The recommended ~~starting~~ dose is 20 mg/day. Although ~~there is a risk of an increase in adverse effects at doses greater than 20 mg/day, an increase in dosage can be considered if there is no response after three weeks of treatment~~ the risk of adverse effects increases with the dose, a gradual increase in the dosage can be considered in some patients with insufficient response to the dosage of 20 mg/day after two weeks, up to a maximum of 60 mg/day. If no improvement is observed within 10 weeks, treatment with fluoxetine should be reconsidered. If a good therapeutic response has been obtained, treatment can be continued at a dosage adjusted on an individual basis. While there are no studies to answer the question of how long to continue fluoxetine treatment, OCD is a chronic condition and it is reasonable to consider continuation beyond 10 weeks in responding patients. Dosage adjustments should be made carefully on an individual patient basis, to maintain the patient at the lowest effective dose. The need for treatment should be reassessed periodically. Some clinicians advocate concomitant behavioural psychotherapy for patients who have done well on pharmacotherapy.

	patients who have done well on pharmacotherapy. Long-term efficacy (more than 24 weeks) has not been demonstrated in obsessive compulsive disorder. **Bulimia** Adults and the elderly: a dosage of 60 mg/day is recommended. Long-term efficacy (more than 3 months) has not been demonstrated in bulimia. **All indications:** The recommended dose may be increased or decreased. Doses above 80 mg/day have not been evaluated. Fluoxetine can be administered in one or more daily doses, during or between meals. If treatment is stopped, the active substances persist in the body for several weeks. This should be borne in mind when starting or stopping treatment. A gradual reduction in treatment is not needed in most patients. The capsule and dispersible tablet forms are bioequivalent. **Children** Since efficacy and safety have not been studied in children and adolescents (under 18 years), the use of fluoxetine in this age group is not recommended (see 4.4 Special warnings and precautions for use). **Elderly patients:** Caution is recommended when increasing the dose, and the daily dose should generally not exceed 40 mg. However, the maximum recommended dose is 60 mg/day. A dose of less than 20 mg/day or a less frequent dose (e.g. 20 mg every second day) should be considered in patients with hepatic impairment (see section 5.2), or in patients where concomitant medication has the potential for interaction with PROZAC (see section 4.5).	Long-term efficacy (more than 24 weeks) has not been demonstrated in obsessive compulsive disorder. **Bulimia** *Adults and the elderly* ~~Adults and the elderly:~~ A dosage of 60 mg/day is recommended. Long-term efficacy (more than 3 months) has not been demonstrated in bulimia. **Adults - all indications** The recommended dose may be increased or decreased. Doses above 80 mg/day have not been evaluated. Fluoxetine can be administered in one or more daily doses, during or between meals. If treatment is stopped, the active substances persist in the body for several weeks. This should be borne in mind when stopping or stopping treatment. ~~A gradual reduction in treatment is not needed in most patients.~~ The capsule and dispersible tablet forms are bioequivalent. **Children and adolescents aged 8 years and above – (Moderate to severe major depressive episode)** ~~*Since efficacy and safety have not been studied in children and adolescents (under 18 years), the use of fluoxetine in this age group is not recommended (see 4.4 Special warnings and precautions for use).*~~ Treatment should be initiated and monitored under specialist supervision. The starting dose is 10 mg/day given as 2.5 ml of PROZAC 20 mg/5 ml oral solution. Dosage adjustments should be made carefully on an individual patient basis, to maintain the patient at the lowest effective dose. After one to two weeks, the dose may be increased to 20 mg/day. Clinical trial experience with daily doses greater than 20 mg/day is minimal. There are only limited data on treatment periods greater than 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). For children and adolescents who respond to treatment, the need for continued treatment after 6 months should be reviewed. If no clinical benefit is achieved within the first 9 weeks, treatment should be reconsidered. **Elderly patients:** Caution is recommended when increasing the dose, and the daily dose should generally not exceed 40 mg. However, the maximum recommended dose is 60 mg/day. A dose of less than 20 mg/day or a less frequent dose (e.g. 20 mg every second day) should be considered in patients with hepatic impairment (see section 5.2), or in patients where concomitant medication has the potential for interaction with fluoxetine (see section 4.5). **Withdrawal symptoms seen on discontinuation of PROZAC:**

		Abrupt discontinuation of treatment should be avoided. When stopping treatment with PROZAC the dose should be gradually reduced over a period of at least one to two weeks in order to reduce the risk of withdrawal reactions (see sections 4.4 and 4.8). If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, resuming the previously prescribed dose may be considered. Subsequently, the physician may continue decreasing the dose, but at a more gradual rate.
4.2 Posology and method of administration "variation of 16.01.12"	**1 Children and adolescents aged 8 years and above – (Moderate to severe major depressive episode)** […] 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). For children and adolescents who respond to treatment, the need for continued treatment after 6 months should be reviewed. If no clinical benefit is achieved within the first 9 weeks, treatment should be reconsidered. […]	**2 Children and adolescents aged 8 years and above – (Moderate to severe major depressive episode)** […] 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). For ~~children and adolescents~~ paediatric patients who respond to treatment, the need for continued treatment after 6 months should be reviewed. If no clinical benefit is achieved within the first 9 weeks, treatment should be reconsidered. […]
4.3. Contra-indications "variation of 07.02.13"	**3 Monoamine oxidase inhibitors (MAOIs):** Serious reactions, sometimes fatal, have been reported in patients receiving treatment combining an SSRI (selective serotonin reuptake inhibitor) with an MAOI (monoamine oxidase inhibitor) and in patients who started treatment with an MAOI who have recently discontinued their SSRI treatment. Treatment with fluoxetine cannot be started until two weeks after discontinuation of a non-selective MAOI.	**4 Monoamine oxidase inhibitors (MAOIs):** Serious reactions, sometimes fatal, have been reported in patients receiving treatment combining an SSRI (selective serotonin reuptake inhibitor) with an MAOI (monoamine oxidase inhibitor) and in patients who started treatment with an MAOI who have recently discontinued their SSRI treatment. Treatment with fluoxetine cannot be started until two weeks after discontinuation of a non-selective MAOI and the following day after discontinuation of a reversible MAOI-A. **5**
4.3. Contra-indications "variation of 07.08.13"	**Hypersensitivity to fluoxetine or to any of the excipients.** **6 Monoamine oxidase inhibitors (MAOIs):** […] Consequently, fluoxetine is contraindicated in combination with a non-selective MAOI. Similarly, a period of at least 5 weeks should elapse between discontinuing treatment with fluoxetine and initiating treatment with MAOI. If fluoxetine has been prescribed chronically and/or in high doses, a longer interval must be considered. Combining fluoxetine with a reversible MAOI is not recommended. However, treatment with fluoxetine can be initiated the day after discontinuing treatment with a reversible MAOI (such as moclobemide). **7**	**Hypersensitivity to fluoxetine or to any of the excipients.** **8 Monoamine oxidase inhibitors (MAOIs):** […] Consequently, fluoxetine is contraindicated in combination with a non-selective MAOI. Similarly, a period of at least 5 weeks should elapse between discontinuing treatment with fluoxetine and initiating treatment with MAOI. If fluoxetine has been prescribed chronically and/or in high doses, a longer interval must be considered. Combining fluoxetine with a reversible MAOI (such as moclobemide, linezolid, methylthioninium chloride (also called methylene blue; a non-selective reversible MAOI indicated in the treatment of methaemoglobinaemia)) is not recommended. ~~However, t~~Treatment with fluoxetine can be initiated the day after discontinuing treatment with a reversible MAOI ~~(such as moclobemide)~~. **9** Under certain exceptional circumstances, linezolid (an antibiotic, nonselective reversible MAOI) can be given in combination with fluoxetine provided that close monitoring of the symptoms of serotonin syndrome and blood pressure can be guaranteed.

4.4 Special warnings and precautions for use "variation of 06.12.07"	**Warnings** *Use in children and adolescents under 18 years of age* The use of PROZAC is not recommended in children and adolescents under 18 years of age. Suicidal behaviour (attempted suicide and suicidal thoughts) and hostility (mainly aggression, oppositional behaviour and anger) were more frequently observed during clinical studies in children and adolescents treated with antidepressants than in 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, there are no long-term safety data in children and adolescents concerning growth, maturation and cognitive and behavioural development. *Rash and allergic reactions* Rash, anaphylactoid reactions and progressive systemic symptoms, sometimes serious (involving the skin, kidneys, liver or lungs) have been reported. On the appearance of a rash or any other allergic symptom for which no other aetiology can be identified, fluoxetine should be discontinued. **Precautions for use** *Seizures* Seizures are a potential risk with antidepressant treatment. Consequently, as with other antidepressants, treatment with fluoxetine should be initiated cautioously in patients with a history of epilepsy. Treatment should be discontinued in any patient with an epileptic seizure or increased seizure frequency. Fluoxetine should be avoided in patients with unstable epilepsy; close monitoring is needed in patients with controlled epilepsy. *Mania* Antidepressants should be used with caution in patients with a history of mania/hypomania. As with any antidepressant, treatment with fluoxetine should be discontinued in patients who are in a manic state. *Hepatic/renal function* Fluoxetine is extensively metabolised by the liver and eliminated by the kidneys. A dosage	**Warnings** *Use in children and adolescents under 18 years of age* ~~The use of PROZAC is not recommended in children and adolescents under 18 years of age.~~ Suicidal behaviour (attempted suicide and suicidal thoughts) and hostility (mainly aggression, oppositional behaviour and anger) were more frequently observed during clinical studies in children and adolescents treated with antidepressants than in those treated with placebo. PROZAC should not be used in children and adolescents aged 8 to 18 years except in the treatment of a moderate to severe major depressive episode (i.e. a clear episode). PROZAC is not recommended in any other indication. 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, ~~there are no~~ long-term safety data in children and adolescents ~~concerning~~, including effects on growth, sexual maturation and cognitive, emotional and behavioural development are limited (see section 5.3). In a 19-week clinical trial, decreased height and weight gain was observed in children and adolescents treated with fluoxetine (see section 4.8). An effect on final adult height has not been established. The possibility of a delay in puberty cannot be ruled out (see sections 4.8 and 5.3). Growth and pubertal development (height, weight and Tanner staging) should therefore be monitored during and after treatment with fluoxetine. If growth or pubertal development is slowed, referral to a paediatrician should be considered. In clinical trials in paediatrics, cases of manic and hypomanic episodes have commonly been reported (see section 4.8). Consequently, regular monitoring for the occurrence of a manic or hypomanic episode is recommended. Treatment with fluoxetine should be discontinued in any patient showing the first signs of mania or hypomania. It is essential for the prescribing doctor to discuss in depth the risks and benefits of treatment with the child or the adolescent and/or his/her parents. *Rash and allergic reactions* Rash, anaphylactoid reactions and progressive systemic symptoms, sometimes serious (involving the skin, kidneys, liver or lungs) have been reported. On the appearance of a rash or any other allergic symptom for which no other aetiology can be identified, fluoxetine should be discontinued. **Precautions for use** *Seizures* Seizures are a potential risk with antidepressant treatment. Consequently, as with other antidepressants, treatment with fluoxetine should be ~~initiated~~ started cautiously in patients with a history of epilepsy. Treatment should be discontinued in any patient with an epileptic seizure or increased seizure frequency. Fluoxetine must be avoided in patients with unstable epilepsy; close monitoring is needed in patients with controlled epilepsy. *Mania* Antidepressants should be used with caution in patients with a history of mania/hypomania. As with any antidepressant, treatment with fluoxetine should be discontinued in patients who are in a manic state. *Hepatic/renal function* Fluoxetine is extensively metabolised by the liver and eliminated by the kidneys. A dosage of less than 20 mg/day or a less frequent dose (every second day, for example) is recommended in patients with

	of less than 20 mg/day or a less frequent (every second day, for example) is recommended in patients with hepatic failure. In patients with severe renal failure (GFR < 10 ml/min) requiring dialysis and treated with fluoxetine at a dosage of 20 mg/day for 2 months, no difference in the plasma concentrations of fluoxetine or norfluoxetine was observed by comparison with checks carried out in patients with normal renal function. *Heart disease* No conduction abnormality leading to heart block was observed in the ECGs performed in 312 patients who received fluoxetine in double-blind clinical studies. However, since clinical experience is limited in patients with acute heart disease, caution is recommended. *Weight loss* Weight loss may occur in patients treated with fluoxetine, but this slimming is generally proportional to baseline body weight. *Diabetes* In patients with diabetes, treatment with an SSRI may alter glycaemic control. Hypoglycaemia during treatment and hyperglycaemia following discontinuation have been reported. The dosage of insulin and/or the oral antidiabetic may need to be adjusted. *Suicide* As with any antidepressant treatment, improvement may not occur during the first few weeks of treatment; close clinical monitoring of patients is therefore needed at the start of treatment. The possibility of attempted suicide is inherent in depression and the risk may persist until significant remission occurs. Clinical experience has shown that when treating depression and whatever the treatment used, the risk of suicide may increase at the start of treatment. *Haemorrhage* Cases of cutaneous bleeding such as ecchymosis and purpura have been reported during treatment with SSRIs. Ecchymosis has been reported as an uncommon adverse effect during treatment with fluoxetine. Other haemorrhagic manifestations (e.g. gynaecological haemorrhages, gastrointestinal bleeding and other cutaneous or mucous bleeding) have been reported rarely. Special care is recommended with patients treated with SSRIs, particularly those concomitantly receiving oral anticoagulants, medicines affecting platelet function (e.g. atypical antipsychotics such as clozapine, phenothiazines, most tricyclic antidepressants, acetylsalicylic acid and NSAIDs) or with other medicines that may increase the risk of bleeding, and in patients with a history of bleeding disorders." *Electroconvulsive therapy (ECT)* A few rare cases prolonged seizures have been reported in patients treated with fluoxetine and ECT; special care is therefore recommended. *St John's wort* An increase in serotonergic effects constituting serotonin syndrome may occur when SSRIs are combined with St John's wort (*Hypericum perforatum*).	hepatic failure. In patients with severe renal failure (GFR < 10 ml/min) requiring dialysis and treated with fluoxetine at a dosage of 20 mg/day for 2 months, no difference in the plasma concentrations of fluoxetine or norfluoxetine was observed by comparison with checks carried out in patients with normal renal function. *Heart disease* No conduction abnormality leading to heart block was observed in the ECGs performed in 312 patients who received fluoxetine in double-blind clinical studies. However, since clinical experience is limited in patients with acute heart disease, caution is recommended. *Weight loss* Weight loss may occur in patients treated with fluoxetine, but this slimming is generally proportional to baseline body weight. *Diabetes* In patients with diabetes, treatment with an SSRI may alter glycaemic control. Hypoglycaemia during treatment and hyperglycaemia following discontinuation have been reported. The dosage of insulin and/or the oral antidiabetic may need to be adjusted. *Suicide/suicidal thoughts* ~~As with any antidepressant treatment, the improvement may not occur during the first few weeks of treatment; close clinical monitoring of patients is therefore needed at the start of treatment. The possibility of attempted suicide is inherent in depression and the risk may persist until significant remission occurs. Clinical experience has shown that when treating depression and whatever the treatment used, the risk of suicide may increase at the start of treatment.~~ Depression is associated with an increased risk of suicidal thoughts, self-harm and suicide (suicide-related behaviour). This risk persists until significant remission occurs. As improvement may not occur during the first few weeks or more of treatment, patients should be monitored closely until such improvement occurs. Clinical experience shows that the risk of suicide may increase in the early stages of recovery. Other psychiatric conditions for which PROZAC is prescribed may also be associated with an increased risk of suicide-related behaviour. In addition, these disorders may be co-morbid with a major depressive episode. Patients treated for these other psychiatric disorders should be subject to the same precautions as those applied to patients treated for a major depressive episode. Patients with a history of suicide-related behaviour, those exhibiting a substantial level of suicidal thoughts prior to commencement of treatment are known to be at greater risk of suicidal thoughts or suicide attempts, and should be closely monitored during their treatment. In addition, the risk of suicidal behaviour is increased in young adults. Patients (and their caregivers) should be alerted to the need to monitor for the appearance of any such events and to seek medical advice immediately if these symptoms appear. *Akathisia/psychomotor restlessness* The use of fluoxetine may lead to the development of akathisia, characterised by agitation that is perceived as unpleasant or distressing and by the need to be constantly moving, often combined with an inability to sit or stand still. These symptoms occur most commonly during the first few weeks of treatment. Increasing the dosage may be prejudicial to patients who develop these symptoms.

	Serotonin syndrome or events such as neuroleptic malignant syndrome have been reported rarely during treatment with fluoxetine, particularly in combination with other serotonergic medicines (such as L-tryptophan) and/or with neuroleptics. Since these syndromes may be life-threatening for the patient, treatment with fluoxetine should be discontinued if such events occur (characterised by the concomitant presence of symptoms such as hyperthermia, rigidity, myoclonus, dysfunction of the autonomic nervous system with possible rapid fluctuations of vital signs, altered mental state with confusion, irritability, extreme agitation progressing to delirium and coma) and supportive symptomatic treatment should be initiated.	*Withdrawal symptoms seen on discontinuation of SSRI treatment* Withdrawal symptoms on discontinuation of treatment are common, particularly if discontinuation is abrupt (see section 4.8). In clinical trials, adverse effects on discontinuation of treatment affected about 60% of patients in each of the two groups treated with fluoxetine or placebo. These adverse effects were severe in 17% of cases in the fluoxetine group and 12% of cases in the placebo group. The risk of withdrawal symptoms may be dependent on several factors including the duration and dose of treatment and the rate of dose reduction. The most commonly reported reactions were as follows: dizziness, sensory disturbances (including paraesthesia), sleep disturbances (including insomnia and intense dreams), asthenia, agitation or anxiety, nausea and/or vomiting, tremor and headache. These symptoms are generally mild to moderate, but may be severe in some patients. They usually appear within the first few days of discontinuing treatment. They generally resolve spontaneously and usually disappear within 2 weeks, although in some patients they may be prolonged (2-3 months or more). It is therefore advised that the dosage of PROZAC should be gradually reduced over a period of at least one to two weeks, according to the patient's needs (see section 4.2, "Withdrawal symptoms seen on discontinuation of treatment with PROZAC"). *Haemorrhage* Cases of cutaneous bleeding such as ecchymosis and purpura have been reported during treatment with SSRIs. Ecchymosis has been reported as an uncommon adverse effect during treatment with fluoxetine. Other haemorrhagic manifestations (e.g. gynaecological haemorrhages, gastrointestinal bleeding and other cutaneous or mucous bleeding) have been reported rarely. Special care is recommended with patients treated with SSRIs, particularly those concomitantly receiving oral anticoagulants, medicines affecting platelet function (e.g. atypical antipsychotics such as clozapine, phenothiazines, most tricyclic antidepressants, acetylsalicylic acid and NSAIDs) or with other medicines that may increase the risk of bleeding, and in patients with a history of bleeding disorders." *Electroconvulsive therapy (ECT)* A few rare cases of prolonged seizures have been reported in patients treated with fluoxetine and ECT; special care is therefore recommended. *St John's wort* An increase in serotonergic effects constituting serotonin syndrome may occur when SSRIs are combined with St John's wort (*Hypericum perforatum*). Serotonin syndrome or events such as neuroleptic malignant syndrome have been reported rarely during treatment with fluoxetine, particularly in combination with other serotonergic medicines (such as L-tryptophan) and/or with neuroleptics. Since these syndromes may be life-threatening for the patient, treatment with fluoxetine should be discontinued if such events occur (characterised by the concomitant presence of symptoms such as hyperthermia, rigidity, myoclonus, dysfunction of the autonomic nervous system with possible rapid fluctuations of vital ~~signs~~ parameters, altered mental state with ~~confusion~~ confusional syndrome, irritability, major agitation progressing to delirium and coma) and supportive symptomatic treatment should be ~~initiated~~ started.

4.4 Special warnings and precautions for use "variation of 25.11.2008"	*Diabetes* In patients with diabetes, treatment with an SSRI may alter glycaemic control. Hypoglycaemia during treatment and hyperglycaemia following discontinuation have been reported. The dosage of insulin and/or of the oral antidiabetic may need to be adjusted. In patients with diabetes or on a high-carbohydrate diet, take account of the sucrose content (3 g sucrose per 5 ml solution). *Suicide/suicidal thoughts* Depression is associated with an increased risk of suicidal thoughts, self-harm and suicide (suicide-related behaviour). This risk persists until significant remission occurs. Since the improvement may not occur during the first few weeks or more of treatment, patients should be monitored closely until such improvement occurs. Clinical experience shows that the risk of suicide may increase in the early stages of recovery. Other psychiatric conditions for which PROZAC is prescribed may also be associated with an increased risk of suicide-related behaviour. In addition, these disorders may be co-morbid with a major depressive episode. Patients treated for these other psychiatric disorders should be subject to the same precautions as those applied to patients treated for major depressive episode. Patients with a history of suicide-related behaviour, those with a substantial level of suicidal ideation prior to commencement of treatment are known to be at greater risk of suicidal thoughts or suicide attempts, and must be closely monitored during their treatment. In addition, the risk of suicidal behaviour is increased in young adults. Patients (and their caregivers) should be alerted to the need to monitor for the appearance of any such events and to seek medical advice immediately if these symptoms appear. **[…]**	*Diabetes* In patients with diabetes, treatment with an SSRI may alter glycaemic control. Hypoglycaemia during treatment and hyperglycaemia following discontinuation have been reported. The dosage of insulin and/or of the oral antidiabetic may need to be adjusted. ~~**In patients with diabetes or on a high-carbohydrate diet, take account of the sucrose content (3 g sucrose per 5 ml solution).**~~ *Suicide/suicidal thoughts or clinical worsening* Depression is associated with an increased risk of suicidal thoughts, ~~self-harm and suicide~~ self-harm and suicide (suicide-related behaviour). This risk persists until significant remission occurs is achieved. ~~Since the As the~~ Clinical improvement may not occur ~~during the first few weeks or more~~ for several weeks of treatment, patients will need to ~~should~~ be monitored closely until such improvement occurs. Clinical experience shows that the risk of suicide may increase in the early stages of recovery. Other psychiatric conditions ~~for~~ in which PROZAC is prescribed may also be associated with an increased risk of suicide-related behaviour. In addition, these disorders may be co-morbid with a major depressive episode. ~~Patients treated for these other psychiatric disorders should be subject to the same precautions as those applied to patients treated for major depressive episode.~~ The same precautions for use as those mentioned for patients with major depressive disorder should therefore be observed when treating patients with other psychiatric disorders. Patients with a history of suicidal behaviour~~,~~ or those ~~showing~~ expressing ~~a substantial degree~~ significant suicidal thoughts before ~~the initiation of~~ starting treatment~~, are known to have posing~~ are at ~~greater~~ higher risk ~~of suicidal thoughts or suicide attempts~~ of having suicidal thoughts and suicide-related behaviour, and must ~~be monitored closely~~ be monitored closely during ~~their~~ treatment. A meta-analysis of placebo-controlled clinical trials of antidepressant drugs in adult patients with psychiatric disorders showed an increased risk of suicidal behaviour with antidepressants compared with placebo in patients less than 25 years old. ~~In addition, the risk of suicidal behaviour is increased in young adults.~~ Close supervision of patients and in particular those at high risk should accompany drug therapy especially in early treatment, and following dose changes. Patients (and ~~those looking after them~~ their caregivers)~~, must~~ will have to be ~~alerted to~~ warned of the need to monitor for ~~the appearance of such events and ask for medical advice immediately if such symptoms appear~~ the occurrence of clinical worsening, the appearance of suicidal thoughts/behaviour and any abnormal change in behaviour and to take medical advice immediately if these symptoms occur. **[…]**
4.4 Special warnings and precautions for use "variation of 23.09.11»	[…] *Seizures* Seizures are a potential risk with antidepressant treatment. Consequently, as with other antidepressants, treatment with fluoxetine should be initiated cautiously in patients with a history of epilepsy. Treatment shouldt be discontinued in any patient with an epileptic seizure or increased seizure frequency. Fluoxetine should be avoided in patients with unstable epilepsy; close monitoring is needed in patients with controlled epilepsy. *Mania* Antidepressants should be used with caution in patients with a history of mania/hypomania. As with any antidepressant, treatment with fluoxetine should be discontinued in patients who are in a manic state. *Hepatic/renal function*	**Special warnings** […] **Precautions for use** *Seizures* Seizures are a potential risk with antidepressant treatment. Consequently, as with other antidepressants, treatment with fluoxetine should be initiated with caution in patients with a history of epilepsy. Treatment should be discontinued in any patient with an epileptic seizure or increased seizure frequency. Fluoxetine should be avoided in patients with unstable epilepsy; close monitoring is needed in patients with controlled epilepsy. *Mania* Antidepressants should be used with caution in patients with a history of mania/hypomania. As with any antidepressant, treatment with fluoxetine should be discontinued in patients who are in a manic state. *Hepatic/renal function* Fluoxetine is extensively metabolised by the liver and eliminated by the kidneys. A dosage of less than 20 mg/day or a less frequent dose (every second day, for example) is recommended in patients with

	Fluoxetine is extensively metabolised by the liver and eliminated by the kidneys. A dosage of less than 20 mg/day or a less frequent dose (every second day, for example) is recommended in patients with hepatic failure. In patients with severe renal failure (GFR < 10 ml/min) requiring dialysis and treated with fluoxetine at a dosage of 20 mg/day for 2 months, no difference in the plasma concentrations of fluoxetine or norfluoxetine was observed by comparison with checks carried out in patients with normal renal function.	hepatic failure. In patients with severe renal failure (GFR < 10 ml/min) requiring dialysis and treated with fluoxetine at a dosage of 20 mg/day for 2 months, no difference in the plasma concentrations of fluoxetine or norfluoxetine was observed by comparison with checks carried out in patients with normal renal function. *Tamoxifen* Fluoxetine, a potent inhibitor of CYP2D6, may lead to reduced concentrations of endoxifen, one of the most important active metabolites of tamoxifen. Consequently, fluoxetine should as far as possible be avoided during treatment with tamoxifen (see section 4.5).
4.4 Special warnings and precautions for use "variation of 16.01.12"	*Use in children and adolescents under 18 years of age* […] In a 19-week clinical trial, decreased height and weight gain was observed in children and adolescents treated with fluoxetine (see section 4.8). An effect on final adult height has not been established. The possibility of a delay in puberty cannot be ruled out (see sections 4.8 and 5.3). Growth and pubertal development (height, weight and Tanner staging) should therefore be monitored during and after treatment with fluoxetine. If growth or pubertal development is slowed, the advice of a paediatrician should be sought. **Precautions for use** […] *Haemorrhage* Cases of cutaneous bleeding such as ecchymosis and purpura have been reported during treatment with SSRIs. Ecchymosis has been reported as an uncommon adverse effect during treatment with fluoxetine. Other haemorrhagic manifestations (e.g. gynaecological haemorrhages, gastrointestinal bleeding and other cutaneous or mucous bleeding) have been reported rarely instances. Special care is recommended with patients treated with SSRIs, particularly those concomitantly receiving oral anticoagulants, medicines affecting platelet function (e.g.such as atypical antipsychotics such as clozapine, phenothiazines, most tricyclic antidepressants, acetylsalicylic acid and NSAIDs) or with other medicines that may increase the risk of bleeding, and in patients with a history of bleeding disorders." *Electroconvulsive therapy (ECT)* A few rare cases of prolonged seizures have been reported in patients treated with fluoxetine and ECT; special care is therefore recommended.	*Use in children and adolescents under 18 years of age* […] In a 19-week clinical trial, reduced growth in stature and ~~retardation in the growth curve and the~~ weight gain~~curve~~ was observed in children and adolescents treated with fluoxetine (see section 54.1~~8~~). An effect on final adult height has not been established. The possibility of a delay in puberty cannot be ruled out (see sections 4.8 and 5.3). Growth and pubertal development (height, weight and Tanner staging) should therefore be monitored during and after treatment with fluoxetine. If growth or pubertal development is slowed, the advice of a paediatrician should be sought. […] **Precautions for use** […] *Haemorrhage* Cases of cutaneous bleeding such as ecchymosis and purpura have been reported during treatment with SSRIs. Ecchymosis has been reported as an uncommon adverse effect during treatment with fluoxetine. Other haemorrhagic manifestations (e.g. gynaecological haemorrhages, gastrointestinal bleeding and other cutaneous or mucous bleeding) have been reported rarely. Special care is recommended with patients treated with SSRIs, particularly those concomitantly receiving oral anticoagulants, medicines affecting platelet function (e.g. atypical antipsychotics such as clozapine, phenothiazines, most tricyclic antidepressants, acetylsalicylic acid and NSAIDs) or with other medicines that may increase the risk of bleeding, and in patients with a history of bleeding disorders. *Mydriasis* Since cases of mydriasis have been reported with fluoxetine, fluoxetine should be prescribed with caution in patients with raised intraocular pressure or a risk of acute narrow-angle glaucoma. *Electroconvulsive therapy (ECT)* A few rare cases of prolonged seizures have been reported in patients treated with fluoxetine and ECT; special care is therefore recommended.
4.4 Special warnings and precautions for use "variation of 07.02.13"	***Precautions for use*** […] *Tamoxifen* Fluoxetine, a potent inhibitor of CYP2D6, may lead to reduced concentrations of endoxifen, one of the most important active metabolites of tamoxifen. Consequently, fluoxetine should as far as possible be avoided during treatment with tamoxifen (see section 4.5). *Heart disease* No conduction abnormality leading to heart block was observed in the ECGs performed in	***Precautions for use*** […] *Tamoxifen* Fluoxetine, a potent inhibitor of CYP2D6, may lead to reduced concentrations of endoxifen, one of the most important active metabolites of tamoxifen. Consequently, fluoxetine should as far as possible be avoided during treatment with tamoxifen (see section 4.5). ~~*Heart disease*~~*Cardiovascular abnormalities* Cases of QT interval prolongation and ventricular arrhythmia, including torsades de pointes, have been reported since market launch (see sections 4.5, 4.8 and 4.9).

	312 patients who received fluoxetine in double-blind clinical studies. However, since clinical experience is limited in patients with acute heart disease, caution is recommended.	Fluoxetine must be used with caution in patients with congenital long QT, a family history of QT prolongation or other conditions that predispose to arrhythmia (e.g. hypokalaemia, hypomagnesaemia, bradycardia, acute myocardial infarction or uncompensated heart failure) or increased exposure to fluoxetine (e.g. hepatic impairment). If a patient with stable heart disease is treated, an electrocardiogram (ECG) review should be considered before treatment is started. If signs of cardiac arrhythmia appear during treatment with fluoxetine, the treatment should be stopped and an ECG should be performed. ~~No conduction abnormality leading to heart block was observed in the ECGs performed in 312 patients who received fluoxetine in double-blind clinical studies. However, since clinical experience is limited in patients with acute heart disease, caution is recommended.~~
4.5 Interaction with other medicinal products and other forms of interaction "variation of 06.12.07"	**4.5 Interaction with other medicinal products and other forms of interaction** *Half-life:* The long half-lives of fluoxetine and norfluoxetine should be borne in mind (see section 5.2 Pharmacokinetic properties) when considering pharmacodynamic and pharmacokinetic drug interactions (e.g. when switching from fluoxetine treatment to another antidepressant treatment). **Monoamine oxidase inhibitors:** (cf. section 4.3 Contraindications) **Not recommended combination** **+MAOI-A: (cf. section 4.3 Contraindications)** **Combinations requiring precautions for use** **+ MAOI-B (selegiline):** Risk of serotonin syndrome. Clinical monitoring is recommended. **+ Phenytoin:** Changes in plasma levels have been observed when phenytoin was combined with fluoxetine. In some cases, signs of toxicity have appeared. This should be taken into account during the clinical monitoring of the patient and when checking the plasma levels of phenytoin. **+Serotonergic drugs:** Co-administration with serotonergic drugs (e.g. tramadol, triptans) may increase the risk of serotonin syndrome. Use with triptans leads to an additional risk of coronary vasoconstriction and hypertension. **+ Lithium and tryptophan:** Since serotonin syndromes have been reported when SSRIs were taken together with lithium or tryptophan, caution is needed on the concomitant use of fluoxetine with these drugs. Closer and more frequent medical monitoring is required if fluoxetine is combined with lithium. **+ CYP2D6 isoenzyme:** The metabolism of fluoxetine (like that of tricyclic antidepressants and other selective serotonin antidepressants) depends on CYP2D6; concomitant treatment with drugs dependent on this same enzyme system is therefore likely to cause drug interactions. Treatment combining drugs predominantly metabolised by this isoenzyme should be	**4.5 Interaction with other medicinal products and other forms of interaction** **Studies of interactions have been performed only in adults.** *Half-life:* The long half-lives of fluoxetine and norfluoxetine should be borne in mind (see section 5.2 ~~Pharmacokinetic properties~~) when considering pharmacodynamic and pharmacokinetic drug interactions (e.g. when switching from fluoxetine treatment to another antidepressant treatment). **Monoamine oxidase inhibitors:** (~~cf.~~see section 4.3 ~~Contraindications~~) **Not recommended combination** **+MAOI-A: (~~cf.~~ see section 4.3 ~~Contraindications~~)** **Combinations requiring precautions for use** **+ MAOI-B (selegiline):** Risk of serotonin syndrome. Clinical monitoring is recommended. **+ Phenytoin:** Changes in plasma levels have been observed when phenytoin was combined with fluoxetine. In some cases, signs of toxicity have appeared. This should be taken into account during the clinical monitoring of the patient and when checking the plasma levels of phenytoin. **+Serotonergic drugs:** Co-administration serotonergic drugs (e.g. tramadol, triptans) may increase the risk of serotonin syndrome. Use with triptans leads to an additional risk of coronary vasoconstriction and hypertension. **+ Lithium and tryptophan:** Since serotonin syndromes have been reported when SSRIs were taken together with lithium or tryptophan, caution is needed on the concomitant use of fluoxetine with these drugs. Closer and more frequent medical monitoring is required if fluoxetine is combined with lithium. **+ CYP2D6 isoenzyme:** The metabolism of fluoxetine (like that of tricyclic antidepressants and other selective serotonin antidepressants) depends on CYP2D6; concomitant treatment with drugs dependent on this same enzyme system is therefore likely to cause drug interactions. Treatment combining drugs predominantly metabolised by this isoenzyme should be initiated or adjusted to the minimum effective dose when the therapeutic index for this type of drugs is narrow (such as flecainide, encainide, carbamazepine and tricyclic antidepressants). This precaution also applies if fluoxetine has been taken in the previous 5 weeks.

	initiated or adjusted to the minimum effective dose when the therapeutic index for this type of drugs is narrow (such as flecainide, encainide, carbamazepine and tricyclic antidepressants). This precaution also applies if fluoxetine has been taken in the previous 5 weeks. **+ Oral anticoagulants:** Altered anticoagulant effects (laboratory values and/or clinical signs and symptoms), variable according to the case but leading to increased bleeding, have been reported in rare instances when fluoxetine is co-administered with oral anticoagulants. Coagulation monitoring (prothrombin level and INR) should be carried out in patients receiving warfarin when treatment with fluoxetine is initiated or stopped (cf. Special warnings and precautions for use - section 4.4). **+ Electroconvulsive therapy (ECT):** Rare cases of prolonged seizures have been reported in patients on fluoxetine receiving ECT. Care is needed with these patients. **+ Alcohol:** During specific tests, fluoxetine did not lead to any rise in blood alcohol levels or any enhancement of the effects of alcohol. However, alcohol is not recommended during treatment with SSRIs. **+ St John's wort:** An increase in serotonergic effects, such as serotonin syndrome, may occur on the concomitant use of SSRIs and preparations containing St John's wort (*Hypericum perforatum*). **[…]**	**+ Oral anticoagulants:** Altered anticoagulant effects (laboratory values and/or clinical signs and symptoms), variable according to the case but leading to increased bleeding, have been reported in rare instances when fluoxetine is co-administered with oral anticoagulants. Coagulation monitoring (prothrombin level and INR) should be carried out in patients receiving warfarin when treatment with fluoxetine is initiated or stopped (~~cf. Special warnings and precautions for use~~ see section 4.4: *"Haemorrhages"*). **+ Electroconvulsive therapy (ECT):** Rare cases of prolonged seizures have been reported in patients on fluoxetine receiving ECT. Care is needed with these patients. **+ Alcohol:** During specific tests, fluoxetine did not lead to any rise in blood alcohol levels or any enhancement of the effects of alcohol. However, alcohol is not recommended during treatment with SSRIs. **+ St John's wort:** An increase in serotonergic effects, such as serotonin syndrome, may occur on the concomitant use of SSRIs and preparations containing St John's wort (*Hypericum perforatum*). **[…]**
4.5 Interaction with other medicinal products and other forms of interaction "variation of 23.09.11"	[…] **+ CYP2D6 isoenzyme** The metabolism of fluoxetine (like that of tricyclic antidepressants and other selective serotonin antidepressants) depends on CYP2D6; concomitant treatment with drugs dependent on this same enzyme system is therefore likely to cause drug interactions. Treatment combining drugs predominantly metabolised by this isoenzyme should be initiated or adjusted to the minimum effective dose when the therapeutic index for this type of drugs is narrow (such as flecainide, encainide, carbamazepine and tricyclic antidepressants). This precaution also applies if fluoxetine has been taken in the previous 5 weeks.	[…] **+ CYP2D6 isoenzyme** The metabolism of fluoxetine (like that of tricyclic antidepressants and other selective serotonin antidepressants) depends on CYP2D6; concomitant treatment with drugs dependent on this same enzyme system is therefore likely to cause drug interactions. Treatment combining drugs predominantly metabolised by this isoenzyme should be initiated or adjusted to the minimum effective dose when the therapeutic index for this type of drugs is narrow (such as flecainide, encainide, carbamazepine and tricyclic antidepressants). This precaution also applies if fluoxetine has been taken in the previous 5 weeks. A pharmacokinetic interaction between CYP2D6 inhibitors and tamoxifen has been reported in the literature, showing a reduction of 65-75% in the plasma levels of endoxifen, one of the most active metabolites of tamoxifen. In some studies, a reduction in the efficacy of tamoxifen has been reported on the concomitant use of certain SSRI antidepressants. Since a reduction in the effect of tamoxifen cannot be ruled out, combination with powerful CYP2D6 inhibitors (including fluoxetine) should be avoided wherever possible (see section 4.4).

4.5 Interaction with other medicinal products and other forms of interaction "variation of 07.02.13"	**Combinations requiring precautions for use** […] **+ Oral anticoagulants** Altered anticoagulant effects (laboratory values and/or clinical signs and symptoms), variable according to the case but leading to increased bleeding, have been reported in rare instances whenfluoxetine is co-administered with oral anticoagulants. Coagulation monitoring (prothrombin level and INR) should be carried out in patients receiving warfarin when treatment with fluoxetine is initiated or stopped (see section 4.4: *"Haemorrhages"*). **Electroconvulsive therapy (ECT)** Rare cases of prolonged seizures have been reported in patients on fluoxetine receiving ECT. Care is needed with these patients.	**Combinations requiring precautions for use** […] **+ Oral anticoagulants** Altered anticoagulant effects (laboratory values and/or clinical signs and symptoms), variable according to the case but leading to increased bleeding, have been reported uncommonly when fluoxetine is co-administered with oral anticoagulants. Coagulation monitoring (prothrombin level and INR) should be carried out in patients receiving warfarin when treatment with fluoxetine is initiated or stopped (see section 4.4: *"Haemorrhages"*). **+ Electroconvulsive therapy (ECT)** Rare cases of prolonged seizures have been reported in patients on fluoxetine receiving ECT. Care is needed with these patients. **+QT prolongation** No pharmacokinetic or pharmacodynamic studies of fluoxetine combined with treatments prolonging the QT interval have been performed. A cumulative effect of fluoxetine and these treatments cannot be ruled out. Consequently, caution is needed on the co-administration of fluoxetine with treatments prolonging the QT interval, such as Class IA and III antiarrhythmics, antipsychotics (e.g. phenothiazine derivatives, pimozide, haloperidol), tricyclic antidepressants, certain antimicrobials (e.g. sparfloxacin, moxifloxacin, erythromycin IV, pentamidine), antimalarial treatments, particularly halofantrine, and certain antihistamines (astemizole, mizolastine).
4.6. Pregnancy and lactation "variation of 09.07.10"	**Pregnancy** Data from a large number of exposed pregnancies have revealed no teratogenic effect of fluoxetine. Fluoxetine can be used during pregnancy, but special caution is advised particularly at the end of pregnancy or just before delivery, because of effects reported in newborns such as: irritability, tremor, hypotonia, persistent crying, suckling difficulties or sleep disorders. These symptoms may be a sign of serotonergic effects or of withdrawal syndrome. The time to the appearance of or the duration of these symptoms may be linked to the long half-life of fluoxetine (4-6 days) and its active metabolite, norfluoxetine (4-16 days). **Breast-feeding** Fluoxetine and its metabolite norfluoxetine are secreted in breast milk. Adverse effects have been reported in children breast-fed by mothers treated with fluoxetine. If fluoxetine treatment proves necessary, discontinuation of breast-feeding must be considered. However, if breast-feeding is continued, the lowest effective dose of fluoxetine should be prescribed. **[…]**	**Pregnancy** Epidemiological data suggest that the use of SSRIs in pregnancy, particularly in late pregnancy, may increase the risk of persistent pulmonary hypertension of the newborn (PPHN). The observed risk was approximately 5 cases per 1000 pregnancies. In the general population, the risk of PPHN is 1-2 cases per 1000 pregnancies. ~~Data from a large number of exposed pregnancies have revealed no teratogenic effect of fluoxetine.~~ In addition, although fluoxetine can be used during pregnancy, ~~but~~ special caution is advised particularly at the end of pregnancy or just before delivery, because of other effects reported in newborns such as: irritability, tremor, hypotonia, persistent crying, suckling difficulties or sleep disorders. These symptoms may be a sign of serotonergic effects or of withdrawal syndrome. The time to the appearance of or the duration of these symptoms may be linked to the long half-life of fluoxetine (4-6 days) and its active metabolite, norfluoxetine (4-16 days). **Breast-feeding** Fluoxetine and its metabolite norfluoxetine are secreted in breast milk. Adverse effects have been reported in children breast-fed by mothers treated with fluoxetine. If fluoxetine treatment proves necessary, discontinuation of breast-feeding must be considered. However, if breast-feeding is continued, the lowest effective dose of fluoxetine should be prescribed. **[…]**

4.6. Pregnancy and lactation "variation of 29.09.2010"	**Pregnancy** Epidemiological data suggest that the use of SSRIs in pregnancy, particularly in late pregnancy, may increase the risk of persistent pulmonary hypertension of the newborn (PPHN). The observed risk was approximately 5 cases per 1000 pregnancies. In the general population, the risk of PPHN is 1-2 cases per 1000 pregnancies. In addition, although fluoxetine can be used during pregnancy, special caution is advised particularly at the end of pregnancy or just before delivery, because of other effects reported in newborns such as: irritability, tremor, hypotonia, persistent crying, suckling difficulties or sleep disorders. These symptoms may be a sign of serotonergic effects or of withdrawal syndrome. The time to the appearance of or the duration of these symptoms may be linked to the long half-life of fluoxetine (4-6 days) and its active metabolite, norfluoxetine (4-16 days). **Breast-feeding** Fluoxetine and its metabolite norfluoxetine are secreted in breast milk. Adverse effects have been reported in children breast-fed by mothers treated with fluoxetine. If fluoxetine treatment proves necessary, discontinuation of breast-feeding should be considered. However, if breast-feeding is continued, the lowest effective dose of fluoxetine should be prescribed.	**Pregnancy** Some epidemiological studies suggest an increased risk of cardiovascular malformations associated with the use of fluoxetine during the first trimester of pregnancy. The mechanism is not known. Overall, the data suggest that the risk of having a child with a cardiovascular malformation after maternal exposure to fluoxetine is about 2/100, whereas the expected rate for this type of malformations is approximately 1/100 in the general population. Epidemiological data suggest that the use of SSRIs in pregnancy, particularly in late pregnancy, may increase the risk of persistent pulmonary hypertension of the newborn (PPHN). The observed risk was approximately 5 cases per 1000 pregnancies. In the general population, the risk of PPHN is 1-2 cases per 1000 pregnancies. In addition, although fluoxetine can be used during pregnancy, special caution is advised particularly at the end of pregnancy or just before delivery, because of other effects reported in newborns such as: irritability, tremor, hypotonia, persistent crying, suckling difficulties or sleep disorders. These symptoms may be a sign of serotonergic effects or of withdrawal syndrome. The time to the appearance of or the duration of these symptoms may be linked to the long half-life of fluoxetine (4-6 days) and its active metabolite, norfluoxetine (4-16 days). **Breast-feeding** Fluoxetine and its metabolite norfluoxetine are secreted in breast milk. Adverse effects have been reported in children breast-fed by mothers treated with fluoxetine. If fluoxetine treatment proves necessary, discontinuation of breast-feeding should be considered. However, if breast-feeding is continued, the lowest effective dose of fluoxetine should be prescribed.
4.6. Pregnancy and lactation **"variation of 23.09.11"**	**Pregnancy** Some epidemiological studies suggest an increased risk of cardiovascular malformations associated with the use of fluoxetine during the first trimester of pregnancy. The mechanism is not known. Overall, the data suggest that the risk of having a child with a cardiovascular malformation after maternal exposure to fluoxetine is about 2/100, whereas the expected rate for this type of malformations is approximately 1/100 in the general population. […]	**Pregnancy** Some epidemiological studies suggest an increased risk of cardiovascular malformations associated with the use of fluoxetine during the first trimester of pregnancy. The mechanism is not known. Overall, the data suggest that the risk of ~~having a child with a~~ cardiovascular malformation in a child after maternal exposure to fluoxetine is about 2/100, whereas the expected rate for this type of malformations is approximately 1/100 in the general population. […]
4.6. Fertility, pregnancy and lactation "variation of 18.03.13"	[…] **Breast-feeding** Fluoxetine and its metabolite norfluoxetine are secreted into the breast milk. Adverse effects have been reported in children breast-fed by mothers treated with fluoxetine. If fluoxetine treatment proves necessary, discontinuation of breast-feeding should be considered. However, if breast-feeding is continued, the lowest effective dose of fluoxetine should be prescribed.	[…] **Breast-feeding** Fluoxetine and its metabolite norfluoxetine are secreted into the breast milk. Adverse effects have been reported in children breast-fed by mothers treated with fluoxetine. If fluoxetine treatment proves necessary, discontinuation of breast-feeding should be considered. However, if breast-feeding is continued, the lowest effective dose of fluoxetine should be prescribed. **Fertility** Animal data have shown that fluoxetine may affect sperm quality (see section 5.3). Human case reports with some SSRIs have shown that an effect on sperm quality is reversible. No impact on human fertility has been observed so far.

4.8 Undesirable effects "variation of 06.12.07"	Adverse effects may be reduced in intensity and frequency if treatment is continued and do not generally necessitate discontinuation of treatment. As with all SSRIs, the following adverse effects have been reported: **General disorders** Allergic reactions (such as pruritus, rash, urticaria, anaphylactoid reaction, vasculitis, serum sickness, angioedema) (cf. sections 4.3 Contraindications and 4.4 Special warnings and precautions for use), tremor, serotonin syndrome, photosensitivity, very rare cases of Lyell syndrome. **Digestive system** Gastrointestinal disorders (such as diarrhoea, nausea, vomiting, dyspepsia, dysphagia, dysgeusia), dry mouth. Rare abnormalities of hepatic function. Very rare cases of idiosyncratic hepatitis. **Nervous system** Headache, sleep disorders (parasomnia, insomnia, somnolence, etc.), dizziness, anorexia, fatigue, euphoria, transient abnormal movements (tics, ataxia, tremor, myoclonus), convulsions and psychomotor agitation. Very rare cases of serotonin syndromes. **Psychiatric disorders** Hallucinations, manic reaction, confusion, agitation, anxiety and associated symptoms (such as nervousness), disorders of concentration and thought (such as depersonalisation), panic attacks (these symptoms may be due to the disease itself). **Urogenital apparatus** Urinary retention, pollakiuria. Sexual disorders (delayed ejaculation or anejaculation, anorgasmia), priapism, galactorrhoea. **Miscellaneous disorders** Alopecia, yawning, vision disorders (such as blurred vision, mydriasis), excessive sweating, vasodilatation, arthralgia, myalgia, orthostatic hypotension, ecchymosis. Other haemorrhagic manifestations (e.g. gynaecological haemorrhages, gastrointestinal bleeds and other cutaneous or mucous bleeds) have been reported in rare instances (cf. section 4.4 Special warnings and precautions for use - "*Haemorrhages"*). **Hyponatraemia** Rare cases of hyponatraemia (including some with concentrations of less than 110 mmol/l) have been reported. This hyponatraemia is reversible when fluoxetine	Adverse effects may be reduced in intensity and frequency if treatment is continued and do not generally necessitate discontinuation of treatment. As with all SSRIs, the following adverse effects have been reported: **General disorders** Allergic reactions (such as pruritus, rash, urticaria, anaphylactoid reaction, vasculitis, serum sickness, angioedema) (~~cf.~~see sections 4.3 ~~Contraindications~~ and 4.4 ~~Special warnings and precautions for use~~), tremor, serotonin syndrome, photosensitivity, and very rarely erythema multiforme that can progress to Stevens-Johnson syndrome or to toxic epidermal necrolysis (~~very rare cases of~~ Lyell syndrome). **Digestive system** Gastrointestinal disorders (such as diarrhoea, nausea, vomiting, dyspepsia, dysphagia, dysgeusia), dry mouth. Rare abnormalities of hepatic function. Very rare cases of idiosyncratic hepatitis. **Nervous system** Headache, sleep disorders (~~parasomnia,~~ abnormal dreams, insomnia, somnolence, etc.), dizziness, anorexia, fatigue, euphoria, transient abnormal movements (tics, ataxia, tremor, myoclonus), convulsions and rarely psychomotor agitation/akathisia (see section 4.4). Very rare cases of serotonin syndromes. **Psychiatric disorders** Hallucinations, manic reaction, confusion, agitation, anxiety and associated symptoms (such as nervousness), disorders of concentration and thought (such as depersonalisation), panic attacks, suicidal thoughts and behaviour (see section 4.4)(these symptoms may be due to the disease itself). **Urogenital apparatus** Urinary retention, pollakiuria. Sexual disorders (delayed ejaculation or anejaculation, anorgasmia), priapism, galactorrhoea. **Miscellaneous disorders** Alopecia, yawning, vision disorders (such as blurred vision, mydriasis), excessive sweating, vasodilatation, arthralgia, myalgia, orthostatic hypotension, ecchymosis. Other haemorrhagic manifestations (e.g. gynaecological haemorrhages, gastrointestinal bleeds and other cutaneous or mucous bleeds) have been reported in rare instances (~~cf.~~see section 4.4 ~~Special warnings and precautions for use -~~ "*Haemorrhages"*). **Hyponatraemia** Rare cases of hyponatraemia (including some with concentrations of less than 110 mmol/l) have been reported and seem to be reversible on the discontinuation of fluoxetine treatment. ~~This hyponatraemia is reversible when fluoxetine treatment is stopped.~~ Some cases ~~were possibly due to~~ could be linked to inappropriate antidiuretic hormone secretion syndrome. Most cases have been described in elderly

	treatment is stopped. Some cases were possibly due to inappropriate antidiuretic hormone secretion syndrome. Most cases have been described in elderly patients and in patients taking diuretics or hypovolaemics. **Respiratory system** Pharyngitis, dyspnoea. Rare pulmonary disorders (with nonspecific inflammatory histological lesions and/or fibrosis) have been reported. Dyspnoea may be the only warning symptom. Withdrawal symptoms have been reported on the discontinuation of SSRIs; however, they do not seem to have been linked to dependence. Symptoms commonly reported are: dizziness, paraesthesia, anxiety, nausea, headache; most of them are moderate and limited. Fluoxetine has rarely been associated with such symptoms. Since the plasma levels of fluoxetine and norfluoxetine fall gradually when treatment is stopped, it is not necessary to reduce the dosage in most patients.	patients and in patients taking diuretics or hypovolaemics. **Respiratory system** Pharyngitis, dyspnoea. Rare pulmonary disorders (~~with nonspecific inflammatory histological lesions and/or fibrosis~~ including inflammatory processes of different histological types and/or fibrosis) have been reported. Dyspnoea may be the only warning symptom. **Withdrawal symptoms seen on discontinuation of fluoxetine treatment** ~~Withdrawal symptoms have been reported on the discontinuation of SSRIs; however, they do not seem to have been linked to dependence.~~ Discontinuing treatment with fluoxetine often causes withdrawal symptoms. Symptoms~~The most~~ commonly reported ~~reactions~~ are as follows: dizziness, sensory disturbances (including paraesthesia), sleep disturbances (including insomnia and intense dreams), asthenia, agitation or anxiety, nausea and/or vomiting, tremor and headache~~; most of them are moderate and limited. Fluoxetine has rarely been associated with such symptoms.~~ These symptoms are generally mild to moderate and often resolve spontaneously, although they can be severe and/or prolonged in some patients (see section 4.4). It is therefore necessary to gradually reduce the doses when treatment with PROZAC is no longer needed (see sections 4.2 and 4.4). ~~Since the plasma levels of fluoxetine and norfluoxetine fall gradually when treatment is stopped, it is not necessary to reduce the dosage in most patients.~~ **Children and adolescents (see section 4.4)** Suicidal behaviour (attempted suicide and suicidal thoughts) and hostility were more commonly observed during clinical studies in children and adolescents treated with antidepressants than in those treated with placebo. The safety of fluoxetine has not been systematically assessed over more than 19 weeks of treatment. In clinical studies carried out in paediatrics, cases of manic reactions, including mania and hypomania, were reported (2.6% in the group of patients treated with fluoxetine versus 0% in the placebo group), leading to discontinuation of treatment in most cases. These patients did not have any history of hypomanic/manic episodes. In a 19-week clinical study, children and adolescents treated with fluoxetine showed decreased height and weight gain (on average, -1.1 cm in height (p=0.004) and -1.1 kg in weight (p=0.008) versus the placebo group). Isolated cases of slowed growth have also been reported during clinical experience. Isolated cases of adverse effects suggesting retardation of sexual maturation or sexual dysfunction have been reported during clinical experience in paediatrics (see section 5.3). In clinical studies in paediatrics, treatment with fluoxetine was associated with a reduction in alkaline phosphatase levels. **[...]**

<table>
<tr><td>4.8 Undesirable effects “variation of 25.11.08”</td><td><u>General disorders</u>
Allergic reactions (such as pruritus, rash, urticaria, anaphylactoid reaction, vasculitis, serum sickness, angioedema) (see sections 4.3 and 4.4), tremor, serotonin syndrome, photosensitivity, very rare cases of Lyell syndrome.
[…]
<u>Psychiatric disorders</u>
Hallucinations, manic reaction, confusion, agitation, anxiety and associated symptoms (such as nervousness), disorders of concentration and thought (such as deperson-alisation), panic attacks, suicidal thoughts and behaviour (these symptoms may be due to the disease itself).</td><td><u>General disorders</u>
Allergic reactions (such as pruritus, rash, urticaria, anaphylactoid reaction, vasculitis, serum sickness, angioedema) (see sections 4.3 and 4.4), <s>tremor</s>, chills, serotonin syndrome, photosensitivity, and very rarely erythema multiforme that can progress to Stevens-Johnson syndrome or to toxic epidermal necrolysis (<s>rare cases of</s> Lyell syndrome).
[…]
<u>Psychiatric disorders</u>
Hallucinations, manic reaction, confusion, agitation, anxiety and associated symptoms (such as nervousness), disorders of concentration and thought (such as depersonalisation), panic attacks, suicidal thoughts and behaviour (see section 4.4)(these symptoms may be due to the disease itself).
Cases of suicidal thoughts and behaviour have been reported during treatment with fluoxetine or shortly after its discontinuation (see section 4.4).</td></tr>
<tr><td>4.8 Undesirable effects “variation of 09.07.10”</td><td>[…]

<u>Respiratory system</u>
Pharyngitis, dyspnoea. Rare pulmonary disorders (with inflammatory processes of different histological types and/or fibrosis) have been reported. Dyspnoea may be the only warning symptom.</td><td>[…]

<u>Respiratory system</u>
Pharyngitis, dyspnoea. Rare pulmonary disorders (with processes of different histological types and/or fibrosis) have been reported. Dyspnoea may be the only warning symptom.

<u>Bone fractures</u>

Epidemiological studies, performed mainly in patients aged 50 years or over, show an increased risk of bone fractures in patients receiving selective serotonin reuptake inhibitors (SSRIs) or tricyclic antidepressants (TCAs). The mechanism leading to this risk is unknown.</td></tr>
<tr><td>4.8 Undesirable effects “variation of 23.09.11 and of 23.11.2011”</td><td>Adverse effects may be reduced in intensity and frequency if treatment is continued and do not generally necessitate discontinuation of treatment.
As with all SSRIs, the following adverse effects have been reported:
<u>General disorders</u>
Allergic reactions (such as pruritus, rash, urticaria, anaphylactoid reaction, vasculitis, serum sickness, angioedema) (see sections 4.3 and 4.4), tremor, serotonin syndrome, photosensitivity, and very rarely erythema multiforme that can progress to Stevens-Johnson syndrome or toxic epidermal necrolysis (Lyell syndrome).
<u>Digestive system</u>
Gastrointestinal disorders (such as diarrhoea, nausea, vomiting, dyspepsia, dysphagia, dysgeusia), dry mouth. Rare abnormalities of hepatic function. Very rare cases of idiosyncratic hepatitis.
<u>Nervous system</u>
Headache, sleep disorders (abnormal dreams, insomnia, somnolence, etc.), dizziness, anorexia, fatigue, euphoria, transient abnormal movements (tics, ataxia, tremor, myoclonus), convulsions and rarely psychomotor agitation/akathisia (see section 4.4). Very rare cases of serotonin syndromes.
<u>Psychiatric disorders</u>
Hallucinations, manic reaction, confusion, agitation, anxiety and associated symptoms (such as nervousness), disorders of concentration and thought (such as deperson-alisation), panic attacks, suicidal thoughts and behaviour (see section 4.4)(these symptoms may be due to the disease itself).
Cases of suicidal thoughts and behaviour have been reported during treatment with fluoxetine or shortly after its discontinuation (see section 4.4).</td><td>The most commonly reported adverse effects in patients treated with fluoxetine were headache, nausea, insomnia, fatigue and diarrhoea. Adverse effects may be reduced in intensity and frequency if treatment is continued and do not generally necessitate discontinuation of treatment.
The table below shows the adverse effects observed in clinical studies (n=9297) and those from spontaneous reporting. Some of these adverse effects are common to other SSRIs.
Estimated frequency: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1000 to <1/100), rare (≥1/10,000 to <1/1000), very rare <1/10,000), not known (cannot be estimated from the available data). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

<table>
<tr><th>Very Common</th><th>Common</th><th>Uncommon</th><th>Rare</th><th>Very rare</th><th>Frequency not known</th></tr>
<tr><td colspan="6"><u>Blood and lymphatic system disorders</u></td></tr>
<tr><td></td><td></td><td></td><td></td><td>Thrombocyto penia</td><td></td></tr>
<tr><td colspan="6"><u>Immune system disorders:</u></td></tr>
<tr><td></td><td></td><td></td><td>Anaphylactic reaction
Serum sickness</td><td></td><td></td></tr>
<tr><td colspan="6"><u>Endocrine disorders</u></td></tr>
</table>
</td></tr>
</table>

Urogenital apparatus

Urinary retention, pollakiuria. Sexual disorders (delayed ejaculation or anejaculation, anorgasmia), priapism, galactorrhoea.

Miscellaneous disorders

Alopecia, yawning, vision disorders (such as blurred vision, mydriasis), excessive sweating, vasodilatation, arthralgia, myalgia, orthostatic hypotension, ecchymosis.

Other haemorrhagic manifestations (e.g. gynaecological haemorrhages, gastrointestinal bleeding and other cutaneous or mucous bleeding) have been reported in rare instances (see section 4.4 *"Haemorrhages"*).

Hyponatraemia

Rare cases of hyponatraemia (including some with concentrations of less than 110 mmol/l) have been reported and seem to be reversible on the discontinuation of fluoxetine treatment. Some cases could be associated with inappropriate antidiuretic hormone secretion syndrome. Most cases have been described in elderly patients and in patients taking diuretics or hypovolaemics.

Respiratory system

Pharyngitis, dyspnoea. Rare pulmonary disorders (with inflammatory processes of different histolological types and/or fibrosis) have been reported. Dyspnoea may be the only warning symptom.

Bone fractures

Epidemiological studies, performed mainly in patients aged 50 years or over, show an increased risk of bone fractures in patients receiving selective serotonin reuptake inhibitors (SSRIs) or tricyclic antidepressants (TCAs). The mechanism leading to this risk is unknown.

Withdrawal symptoms seen on discontinuation of fluoxetine treatment

Discontinuing treatment with fluoxetine often causes withdrawal symptoms. The most commonly reported reactions are as follows: dizziness, sensory disturbances (including paraesthesia), sleep disturbances (including insomnia and intense dreams), agitation or anxiety, nausea and/or vomiting, tremor and headaches.

These symptoms are generally mild to moderate and often resolve spontaneously, although they can be severe and/or prolonged in some patients (see section 4.4). It is therefore recommended to gradually reduce the doses when treatment with PROZAC is no longer necessary (see sections 4.2 and 4.4).

Children and adolescents (see section 4.4)

Suicidal behaviour (attempted suicide and suicidal thoughts) and hostility were more commonly observed during clinical studies in children and adolescents treated with antidepressants than in those treated with placebo.

The safety of fluoxetine has not been systematically assessed over more than 19 weeks of treatment.

In clinical trials carried out in paediatrics, cases of manic reactions, including mania and hypomania, were reported (2.6% in the group of patients treated with fluoxetine versus 0% in the placebo group), leading to the discontinuation of treatment in most cases. These patients did not have any history of hypomanic/manic episodes.

In a 19-week clinical study, the children and adolescents treated with fluoxetine showed decreased height and weight gain (on average, -1.1 cm in height (p=0.004) and -1.1 kg in weight (p=0.008) versus the placebo group). Isolated cases of slowed growth have also been reported during clinical experience.

Isolated cases of adverse effects suggesting retardation of sexual maturation or sexual dysfunction have been reported during clinical experience in paediatrics (see section 5.3).

					Inappropriate secretion of antidiuretic hormone
Metabolism and nutrition disorders					
	Decreased appetite[1]		Hyponatraemia		
Psychiatric disorders					
Insomnia.[2]	Anxiety Nervousness Restlessness Tension Reduced libido[4] Sleep disorders Abnormal dreams[3]	Depersonalisation. Elevated mood Euphoric mood Abnormal thoughts. Abnormal orgasms[5] Bruxism	Hypomania Mania Hallucinations Agitation Panic attacks		Suicidal thoughts and behaviour[14] Confusion Dysphemia
Nervous system disorders					
Headache	Disturbance in attention Dizziness Dysgeusia Lethargy Somnolence[6] Tremor	Psychomotor hyperactivity Dyskinesia Ataxia. Balance disorder Myoclonus	Convulsions. Akathisia. Buccoglossal dyskinesia		Serotonin syndrome
Eye disorders					
	Blurred vision	Mydriasis			
Ear and labyrinth disorders					
					Tinnitus
Cardiac disorders					
	Palpitations				
Vascular disorders					
	Flushing[7]	Hypotension	Vasculitis Vasodilatation		
Respiratory, thoracic and mediastinal disorders					

In paediatric clinical trials, treatment with fluoxetine was associated with a reduction in alkaline phosphatase levels.

	Yawning	Dyspnoea	Pharyngitis		Pulmonary disorders (inflammatory processes of different histological types and/or fibrosis) Epistaxis
Gastrointestinal disorders					
Diarrhoea Nausea	Vomiting Dyspepsia Dry mouth	Dysphagia	Oesophageal pain		Gastrointestinal haemorrhage
Hepatobiliary disorders					
					Very rare idiosyncratic hepatitis
Skin and subcutaneous tissue disorders					
	Rash[8] Urticaria Pruritus Hyperhidrosis	Alopecia. Increased tendency to bruise. Cold sweats	Angioedema. Ecchymosis Photosensitivity reaction Purpura		Erythema multiforme[13]
Musculoskeletal, connective tissue and bone disorders					
	Arthralgia	Muscle twitching			Myalgia
Renal and urinary disorders					
	Frequent urination[9]	Dysuria	Urinary retention		Micturition disorder
Reproductive system and breast disorders					
	Gynaecological bleeding[11] Erectile dysfunction. Ejaculation disorders[10]	Sexual dysfunction	Galactorrhoea		Priapism
General disorders and administration site conditions					
Fatigue[12]	Nervousness. Chills	Malaise Feeling abnormal Feeling cold Feeling hot			Mucosal haemorrhage
Investigations					
	Weight loss				Abnormal liver function tests

[1] Includes anorexia

[2] Includes early morning awakening, difficulty falling asleep and nocturnal awakening
[3] Includes nightmares
[4] Includes loss of libido
[5] Includes anorgasmia
[6] Includes hypersomnia, sedation
[7] Includes hot flushes
[8] Includes erythema, exfoliative rash, heat rash, rash, erythematous eruption, follicular, generalised, macular rash, maculopapular rash, morbilliform rash, papular rash, pruriginous rash, vesicular rash, umbilical erythema rash
[9] Includes pollakiuria
[10] Includes ejaculation failure, ejaculation dysfunction, premature ejaculation, delayed ejaculation, retrograde ejaculation
[11] Includes cervical haemorrhage, uterine dysfunction, uterine bleeding, genital haemorrhage, menometrorrhagia, menorrhagia, metrorrhagia, polymenorrhoea, postmenopausal haemorrhage, uterine haemorrhage, vaginal haemorrhage
[12] Includes asthenia
[13] May progress to Stevens-Johnson syndrome or toxic epidermal necrolysis (Lyell syndrome)
[14] These symptoms may be due to an underlying disease.

~~As with all SSRIs, the following adverse effects have been reported:~~

~~**General disorders**~~

~~Allergic reactions (such as pruritus, rash, urticaria, anaphylactoid reaction, vasculitis, serum sickness, angioedema) (see sections 4.3 and 4.4), tremor, serotonin syndrome, photosensitivity, and very rarely erythema multiforme that can progress to Stevens-Johnson syndrome or toxic epidermal necrolysis (Lyell syndrome).~~

~~**Digestive system**~~

~~Gastrointestinal disorders (such as diarrhoea, nausea, vomiting, dyspepsia, dysphagia, dysgeusia), dry mouth. Rare abnormalities of hepatic function. Very rare cases of idiosyncratic hepatitis.~~

~~**Nervous system**~~

~~Headache, sleep disorders (abnormal dreams, insomnia, somnolence, etc.), dizziness, anorexia, fatigue, euphoria, transient abnormal movements (tics, ataxia, tremor, myoclonus), convulsions and rarely psychomotor agitation/akathisia (see section 4.4). Very rare cases of serotonin syndromes.~~

~~**Psychiatric disorders**~~

~~Hallucinations, manic reaction, confusion, agitation, anxiety and associated symptoms (such as nervousness), disorders of concentration and thought (such as depersonalisation), panic attacks, suicidal thoughts and behaviour (see section 4.4)(these symptoms may be due to the disease itself).~~

Cases of suicidal thoughts and behaviour have been reported during treatment with fluoxetine or shortly after its discontinuation (see section 4.4).

~~**Urogenital apparatus**~~

~~Urinary retention, pollakiuria. Sexual disorders (delayed ejaculation or ejaculation failure, anorgasmia), priapism, galactorrhoea.~~

~~**Miscellaneous disorders**~~

~~Alopecia, yawning, vision disorders (such as blurred vision, mydriasis), excessive sweating, vasodilatation, arthralgia, myalgia, orthostatic hypotension, ecchymosis.~~

~~Other haemorrhagic manifestations (e.g. gynaecological haemorrhages, gastrointestinal bleeding and other cutaneous or mucous bleeding) have been reported in rare instances (see section 4.4 *"Haemorrhages"*)..~~

~~**Hyponatraemia**~~

~~Rare cases of hyponatraemia (including some with concentrations of less than 110 mmol/l) have been reported and seem to be reversible on the discontinuation of fluoxetine treatment. Some cases could be associated with inappropriate antidiuretic hormone secretion syndrome. Most cases have been described in elderly patients and in patients taking diuretics or hypovolaemics.~~

~~**Respiratory system**~~

<table>
<tr>
<td></td>
<td></td>
<td>~~Pharyngitis, dyspnoea. Rare pulmonary disorders (with inflammatory processes of different histological types and/or fibrosis) have been reported. Dyspnoea may be the only warning symptom.~~
<u>Bone fractures</u>
Epidemiological studies, performed mainly in patients aged 50 years and above, show an increased risk of bone fractures in patients receiving selective serotonin reuptake inhibitors (SSRIs) or tricyclic antidepressants (TCAs). The mechanism leading to this risk is unknown.
<u>Withdrawal symptoms seen on discontinuation of fluoxetine treatment</u>
Discontinuing treatment with fluoxetine often causes withdrawal symptoms. The most commonly reported reactions are as follows: dizziness, sensory disturbances (including paraesthesia), sleep disturbances (including insomnia and intense dreams), agitation or anxiety, nausea and/or vomiting, tremor and headaches.
These symptoms are generally mild to moderate and often resolve spontaneously, although they can be severe and/or prolonged in some patients (see section 4.4). It is therefore recommended to gradually reduce the doses when treatment with PROZAC is no longer necessary (see sections 4.2 and 4.4).
<u>Children and adolescents (see section 4.4)</u>
Additional adverse effects have been observed specifically in this population and are described below.
Suicidal behaviour (attempted suicide and suicidal thoughts) and hostility were more commonly observed during clinical studies in children and adolescents treated with antidepressants than in those treated with placebo.
~~The safety of fluoxetine has not been systematically assessed in more than 19 weeks of treatment.~~
~~In the clinical studies carried out in paediatrics,~~Cases of manic reactions, including mania and hypomania, were reported (2.6% in the group of patients treated with fluoxetine versus 0% in the placebo group), leading to the discontinuation of treatment in most cases. These patients did not have any history of hypomanic/manic episodes.
In a 19-week clinical study, the children and adolescents treated with fluoxetine showed decreased height and weight gain (on average, -1.1 cm in height (p=0.004) and -1.1 kg in weight (p=0.008) versus the placebo group). Isolated cases of growth retardation have also been reported during clinical experience.
In clinical trials in paediatrics, epistaxis was commonly reported, and treatment with fluoxetine was associated with a reduction in alkaline phosphatase levels.
Isolated cases of adverse effects suggesting retardation of sexual maturation or sexual dysfunction have been reported ~~during clinical experience~~ from clinical use in paediatrics (see section 5.3).
~~In clinical studies in paediatrics, treatment with fluoxetine was associated with a reduction in alkaline phosphatase levels.~~
The safety of use of fluoxetine in chronic treatment in this population has not been assessed over more than 19 weeks of treatment.</td>
</tr>
<tr>
<td>4.8. Adverse effects “variation of 16.01.12</td>
<td>[…]
Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.
<table><tr><th>Very Common</th><th>Common</th><th>Uncommon</th><th>Rare</th><th>Very rare</th><th>Frequency not known</th></tr><tr><td colspan="6"><u>Blood and lymphatic system disorders</u></td></tr></table></td>
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</tr>
</table>

				Thrombocytopenia	
Immune system disorders					
			Anaphylactic reaction Serum disease		
Endocrine disorders					
					Inappropriate secretion of antidiuretic hormone
Metabolism and nutrition disorders					
	Decreased appetite[1]		Hyponatraemia		
Psychiatric disorders					
Insomnia[2]	Anxiety Nervousness Impatience Tension. Reduced libido[4] Sleep disturbances Abnormal dreams[3]	Depersonalisation Exaltation Euphoria Abnormal thoughts Abnormal orgasms[5] Bruxism.	Hypomania Mania Hallucinations Agitation Panic attacks		Suicidal thoughts and behaviour[14] Confusion Dysphemia
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Headache	Disturbance in attention Dizziness Dysgeusia Lethargy Somnolence[6] Tremor.	Psychomotor hyperactivity Dyskinesia. Ataxia Balance disorder Myoclonus	Convulsions Akathisia. Buccofacial dyskinesia		Serotonin syndrome
Eye disorders					
	Blurred vision	Mydriasis			
Ear and labyrinth disorders					
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Eye disorders					
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Ear and labyrinth disorders					
					Tinnitus
Cardiac disorders					

Cardiac disorders					
	Palpitations				
Vascular disorders					
	Flushing[7]	Hypotension	Vasculitis. Vasodilatation		
Respiratory, thoracic and mediastinal disorders					
	Yawning.	Dyspnoea	Pharyngitis		Pulmonary disorders (inflammatory processes of different histological types and/or fibrosis) Epistaxis.
Gastrointestinal disorders					
Diarrhoea Nausea	Vomiting Dyspepsia Dry mouth	Dysphagia	Oesophageal pain		Gastrointestinal haemorrhage
Hepatobiliary disorders					
					Very rare idiosyncratic hepatitis
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Vascular disorders					
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General disorders and administration site conditions					
Fatigue[12]	Nervousness Chills	Malaise Feeling abnormal Feeling cold Feeling hot			Mucosal haemorrhage
Investigations					
	Weight loss				Abnormal liver function tests

[…]

Children and adolescents (see section 4.4)

Additional adverse effects have been observed specifically in this population and are described below.

Suicidal behaviour (attempted suicide and suicidal thoughts) and hostility were more commonly observed during clinical studies in children and adolescents treated with antidepressants than in those treated with placebo.

Cases of manic reactions, including mania and hypomania, were reported (2.6% in the group of patients treated with fluoxetine versus 0% in the placebo group), leading to the discontinuation of treatment in most cases. These patients did not have any history of hypomanic/manic episodes.

In a 19-week clinical study, the children and adolescents treated with fluoxetine showed decreased height and weight gain (on average, -1.1 cm in height (p=0.004) and -1.1 kg in weight (p=0.008) versus the placebo group). Isolated cases of slowed growth have also been reported during clinical experience.

In clinical trials in paediatrics, epistaxis was commonly reported, and treatment with fluoxetine was associated with a reduction in alkaline phosphatase levels.

Isolated cases of adverse effects suggesting delayed sexual maturation or sexual dysfunction have been reported from clinical use in paediatrics (see section 5.3). The

Renal and urinary disorders					
	Frequent urination[9]	Dysuria	Urinary retention		Micturition disorder
Reproductive system and breast disorders					
	Gynaecological bleeding[11] Erectile dysfunction. Ejaculation disorders[10]	Sexual dysfunction	Galactorrhoea		Priapism
General disorders and administration site conditions					
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Investigations					
	Weight loss				Abnormal liver function tests

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Children and adolescents (see sections 4.4 and 5.1)

Additional adverse effects have been observed specifically in this population and are described below.

Suicidal behaviour (attempted suicide and suicidal thoughts) and hostility were more commonly observed during clinical studies in children and adolescents treated with antidepressants than in those treated with placebo.

Cases of manic reactions, including mania and hypomania, were reported (2.6% in the group of patients treated with fluoxetine versus 0% in the placebo group), leading to the discontinuation of treatment in most cases. These patients did not have any history of hypomanic/manic episodes.

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In clinical trials in paediatrics, epistaxis was commonly reported, and treatment with fluoxetine was associated with a reduction in alkaline phosphatase levels.

Isolated cases of adverse effects suggesting delayed sexual maturation or sexual dysfunction have been reported from clinical use in paediatrics (see also section 5.3). ~~The safety of use of fluoxetine in chronic treatment in this population has not been assessed beyond 19 weeks of treatment.~~

<table>
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<tr><td>4.8 Undesirable effects “variation of 20.03.12”</td><td>[…]

[9] Includes pollakiuria
[10] Includes ejaculation failure, ejaculation dysfunction, premature ejaculation, delayed ejaculation, retrograde ejaculation
[11] Includes cervical haemorrhage, uterine dysfunction, uterine bleeding, genital haemorrhage, menometrorrhagia, menorrhagia, metrorrhagia, polymenorrhoea, postmenopausal haemorrhage, uterine haemorrhage, vaginal haemorrhage
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[12] Includes asthenia
[13] May progress to Stevens-Johnson syndrome or toxic epidermal necrolysis (Lyell syndrome)
[14] These symptoms may be due to an underlying disease.
[15] Most commonly includes gingival bleeding, haematemesis, haematochezia, rectal haemorrhage, haemorrhagic diarrhoea, melaena and bleeding gastric ulcer.</td></tr>
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Insomnia[2]	Anxiety Nervousness Impatience Tension Reduced libido[4] Sleep disturbances Abnormal dreams[3]	Depersonalisation Exaltation Euphoria Abnormal thoughts Abnormal orgasms[5] Bruxism	Hypomania Mania Hallucinations Agitation Panic attacks		Suicidal thoughts and behaviour[14] Confusion Dysphemia	Insomnia[2]	Anxiety Nervousness Impatience Tension Reduced libido[4] Sleep disturbances Abnormal dreams[3]	Depersonalisation Exaltation. Euphoria. Abnormal thoughts Abnormal orgasms[5] Bruxism	Hypomania Mania Hallucinations Agitation Panic attacks		Suicidal thoughts and behaviour[14] Confusion Dysphemia
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Ear and labyrinth disorders											
					Tinnitus	**Ear and labyrinth disorders**					
											Tinnitus
Cardiac disorders											
	Palpitations					**Cardiac disorders**					
							Palpitations		Ventricular arrhythmia including torsades de pointes. QT interval prolongation in the ECG.		
Vascular disorders						**Vascular disorders**					
	Flushing[7]	Hypotension	Vasculitis Vasodilatation				Flushing[7]	Hypotension	Vasculitis. Vasodilatation		
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Hepatobiliary disorders					
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Fatigue[12]	Nervousness Chills	Malaise Feeling abnormal. Feeling cold Feeling hot			Mucosal haemorrhage
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4.9. Overdose "variation of 07.02.13"	Cases of overdose with fluoxetine alone are usually very mild. The symptoms found are: nausea, vomiting, convulsions, cardiovascular disorders ranging from asymptomatic arrhythmia, pulmonary complaints and central nervous system disorders that can range from agitation to coma. Cases of death attributed to overdose with fluoxetine alone were extremely rare. Monitoring of the heart and vital functions is recommended in addition to symptomatic treatment. There is no specific antidote to fluoxetine. […]	Cases of overdose with fluoxetine alone are usually very mild. The symptoms found are: nausea, vomiting, convulsions, cardiovascular disorders ranging from asymptomatic arrhythmia (including disorders of nodal rhythm and ventricular arrhythmia) or ECG changes indicating prolongation of the QTc interval, to cardiac arrest (including very rare cases of torsades de pointes), pulmonary complaints and central nervous system disorders that can range from agitation to coma. Cases of death attributed to overdose with fluoxetine alone were extremely rare. Monitoring of the heart and vital signs is recommended in addition to symptomatic treatment. There is no specific antidote to fluoxetine. […]
5.1 Pharmaco-dynamic properties "variation of 06.12.07"	**ANTIDEPRESSANTS / SELECTIVE SEROTONIN REUPTAKE INHIBITORS, ATC code: N06AB03.** Fluoxetine is a selective serotonin reuptake inhibitor, and this probably accounts for the mechanism of action. Fluoxetine has practically no affinity for other receptors such as α_1-, α_2- and β-adrenergic, dopaminergic, histaminergic$_1$ (H_1) and muscarinic receptors, and receptors of γ-aminobutyric acid (GABA). **Major depressive episode** Placebo-controlled clinical studies with an active comparator were carried out in patients with a diagnosis of major depressive episode. Fluoxetine proved to be significantly more effective than placebo, as measured by the Hamilton Depression Rating Scale (HAM-D). In these studies, fluoxetine showed a response rate (defined as a reduction of 50% in the HAM-D score) and a remission rate significantly superior to those for placebo. **Obsessive compulsive disorder** In short-term clinical studies carried out (less than 24 weeks), fluoxetine proved to be significantly more effective than placebo. A therapeutic effect at a dosage of 20 mg/day has been demonstrated; however, it was observed that higher dosages (40-60 mg/day)	**Pharmacotherapeutic group: ANTIDEPRESSANTS / SELECTIVE SEROTONIN REUPTAKE INHIBITORS, ATC code: N06AB03.** Fluoxetine is a selective serotonin reuptake inhibitor, and this probably accounts for the mechanism of action. Fluoxetine has practically no affinity for other receptors such as α_1-, α_2- and β-adrenergic, dopaminergic, histaminergic$_1$ (H_1) and muscarinic receptors, and receptors of γ-aminobutyric acid (GABA). **Major depressive episode** Placebo-controlled clinical studies with an active comparator were carried out in patients with a diagnosis of major depressive episode. Fluoxetine proved to be significantly more effective than placebo, as measured by the Hamilton Depression Rating Scale (HAM-D). In these studies, fluoxetine showed a response rate (defined as a 50% decrease in the HAM-D score) and a remission rate significantly superior to those for placebo. **Dose-response ratio** In fixed-dose studies in patients with major depressive episode, a flat dose-response curve is seen, indicating that there is no advantage in terms of efficacy in using higher than the recommended doses. However, clinical experience shows that uptitrating may be beneficial for some patients.

	gave a higher response rate. Long-term clinical studies carried out (three short-term studies in the extension phase and a study on the prevention of relapses) did not confirm long-term efficacy. **Bulimia** During short-term clinical studies (less than 16 weeks) carried out in patients receiving outpatient treatment and fulfilling DSM-III-R diagnostic criteria for bulimia, fluoxetine in a dosage of 60 mg/day was shown to be significantly more effective than placebo in reducing bulimic overeating and vomiting or purging. However, no conclusion can be drawn about the long-term maintenance of efficacy. Two studies versus placebo were carried out in women with premenstrual dysphoric disorder according to the diagnostic criteria of DSM-IV. The patients included had symptoms of sufficient severity to impair social and occupational function and relationships with others. Women on oral contraceptive treatment were excluded from the study. In the first study, a continuous dosage of 20 mg/day was used for a period of 6 cycles and an improvement in the primary efficacy endpoints (irritability, anxiety and dysphoria) was observed. In the second study, intermittent luteal phase dosing (20 mg/day for 14 days) was used for a period of 3 cycles and an improvement in the primary efficacy endpoints ("Daily Record of Severity of Problems" score) was observed. However, these studies do not allow any conclusions to be drawn about the efficacy and appropriate duration of treatment.	**Obsessive compulsive disorder** In short-term clinical studies carried out (less than 24 weeks), fluoxetine proved to be significantly more effective than placebo. A therapeutic effect at a dosage of 20 mg/day has been demonstrated; however, it was observed that higher dosages (40-60 mg/day) gave a higher response rate. Long-term clinical studies carried out (three short-term studies in the extension phase and a study on the prevention of relapses) did not confirm long-term efficacy. **Bulimia** During short-term clinical studies (less than 16 weeks) carried out in patients receiving outpatient treatment and fulfilling DSM-III-R diagnostic criteria for bulimia, fluoxetine in a dosage of 60 mg/day was shown to be significantly more effective than placebo in reducing bulimic overeating and vomiting or purging. However, no conclusion can be drawn about the long-term maintenance of efficacy. Two studies versus placebo were carried out in women with premenstrual dysphoric disorder according to the diagnostic criteria of DSM-IV. The patients included had symptoms of sufficient severity to impair social and occupational function and relationships with others. Women on oral contraceptive treatment were excluded from the study. In the first study, a continuous dosage of 20 mg/day was used for a period of 6 cycles and an improvement in the primary efficacy endpoints (irritability, anxiety and dysphoria) was observed. In the second study, intermittent luteal phase dosing (20 mg/day for 14 days) was used for a period of 3 cycles and an improvement in the primary efficacy endpoints ("Daily Record of Severity of Problems" score) was observed. However, these studies do not allow any conclusions to be drawn about the efficacy and appropriate duration of treatment. ^ **Major depressive episodes (children and adolescents)** Clinical studies versus placebo were carried out in children and adolescents aged 8 years and over. In two pivotal short-term studies, PROZAC at a dose of 20 mg was significantly more effective than placebo, as measured by the reduction in total CDRS-R scores (Childhood Depression Rating Scale-Revised) and the CGI-I score (Clinical Global Impression of Improvement). In both studies, in three different assessments made by child psychiatrists, patients met criteria for moderate to severe major depressive state (DSM-III or DSM-IV criteria). The efficacy observed in the clinical studies carried out with fluoxetine could be linked to the inclusion of a selective patient population (patients who did not spontaneously recover over a period of 3-5 weeks and whose depression persisted despite close monitoring). Efficacy and safety data beyond 9 weeks are limited. The efficacy of fluoxetine was generally moderate. The response rates (primary endpoint, defined as a 30% decrease in the CDRS-R score) showed a statistically significant difference in one of the two pivotal studies (58% for fluoxetine versus 32% for placebo, p=0.013 and 65% for fluoxetine versus 54% for placebo, p=0.093). In these two studies, the mean change in the CDRS-R scores during the trial was 20 for fluoxetine versus 11 for placebo, p=0.002 and 22 for fluoxetine versus 15 for placebo, p<0.001.
5.1. Pharmacodynamic properties "variation of 16.01.12"	**Major depressive episodes (children and adolescents)** […] The response rates (primary endpoint, defined as a 30% decrease in the CDRS-R score) showed a statistically significant difference in one of the two pivotal studies (58% for fluoxetine versus 32% for placebo, p=0.013 and 65% for fluoxetine versus 54% for placebo, p=0.093). In these two studies, the mean change in the CDRS-R scores during the study was 20 for fluoxetine versus 11 for placebo, p=0.002 and 22 for fluoxetine versus 15 for placebo, p<0.001.	**Major depressive episodes (children and adolescents)** […] The response rates (primary endpoint, defined as a 30% decrease in the CDRS-R score) showed a statistically significant difference in one of the two pivotal studies (58% for fluoxetine versus 32% for placebo, p=0.013 and 65% for fluoxetine versus 54% for placebo, p=0.093). In these two studies, the mean change in the CDRS-R scores during the trial was 20 for fluoxetine versus 11 for placebo, p=0.002

		and 22 for fluoxetine versus 15 for placebo, p<0.001. **Effects on growth (children and adolescents), see sections 4.4 and 4.8:** In a 19-week clinical study, paediatric patients treated with fluoxetine showed decreased height (on average, -1.1 cm in height; p = 0.004) and less weight gain (on average -1.1 kg in weight; p=0.008) versus the placebo group. In a retrospective observational study with a matched control group and a mean period of exposure to fluoxetine of 1.8 years, paediatric patients treated with fluoxetine showed no difference in terms of height adjusted in relation to the expected growth in height in the matched, untreated control group (0.0 cm, p=0.9673).
5.2 Pharmacokinetic properties "variation of 06/12/07"	[…] **At-risk population** *Elderly subjects* Pharmacokinetic parameters are not altered in elderly subjects in good health by comparison with young subjects. *Hepatic insufficiency* In patients with hepatic insufficiency (alcoholic cirrhosis), the half-lives of fluoxetine and norfluoxetine are increased, and can reach 7 and 12 days respectively. A lower or less frequent dose should be considered. *Renal insufficiency* After single-dose administration of fluoxetine in patients with mild, moderate or total renal insufficiency (anuria), pharmacokinetic parameters did not change by comparison with healthy subjects. However, after repeated administration an increase in steady-state plateau of plasma concentrations may be observed.	[…] **At-risk population** *Elderly subjects* Pharmacokinetic parameters are not altered in elderly subjects in good health by comparison with young subjects. *Children and adolescents* The mean fluoxetine concentration is approximately twice as high in children as in adolescents, and that of norfluoxetine is 1.5 times higher in children than in adolescents. Steady-state plasma concentrations vary with the body weight of the child and are higher in lower-weight children (see section 4.2). As in adults, fluoxetine and norfluoxetine accumulate in large quantities after repeated oral doses; steady-state concentrations were achieved in 3-4 weeks of daily treatment. *Hepatic insufficiency* In patients with hepatic insufficiency (alcoholic cirrhosis), the half-lives of fluoxetine and norfluoxetine are increased, and can reach 7 and 12 days respectively. A lower or less frequent dose should be considered. *Renal insufficiency* After single-dose administration of fluoxetine in patients with mild, moderate or total renal insufficiency (anuria), the pharmacokinetic parameters did not change by comparison with healthy subjects. However, after repeated administration an increase in steady-state plateau of plasma concentrations may be observed.
5.3. Preclinical safety data "variation of 06.12.07"	Tests performed *in vitro* or in animals revealed no carcinogenic or mutagenic effect or any impairment of reproduction.	Tests performed *in vitro* or in animals revealed no carcinogenic or mutagenic effect ~~or any impairment of reproduction.~~ In a toxicology study in juvenile animals, the administration of a dose of 30 mg/kg/day of fluoxetine hydrochloride to young "CD" rats aged 21-90 days led to irreversible testicular degeneration and necrosis, epididymal epithelial vacuolation, immaturity and inactivity of the female reproductive system, and to a reduction in fertility. Delayed sexual maturation appeared in the males (10 and 30 mg/kg/day) and the females (30 mg/kg/day). The significance of these data for human beings is unknown. Rats receiving a dose of 30 mg/kg also showed femur lengths shorter than those observed in the control group and skeletal muscle degeneration, necrosis and regeneration. At a dose of 10 mg/kg/day in animals, the plasma levels achieved were approximately, for fluoxetine, 0.8 to 8.8 times greater and, for norfluoxetine, 3.6 to 23.2 times greater than those normally observed in

		paediatric patients. At a dose of 3 mg/kg/day, the plasma levels achieved in animals were approximately, for fluoxetine, 0.04 to 0.5 times greater and, for norfluoxetine, 0.3 to 2.1 times greater than those normally observed in paediatric patients. A study performed in young mice showed that inhibition of the serotonin transporter disrupts bone growth. There are no data on whether or not the effect is reversible. These results would appear to be supported by clinical data. Another study in young mice aged 4-21 days showed that inhibition of the serotonin transporter had prolonged effects on behaviour. There are no data on the reversibility of this effect. The clinical relevance of this finding has not been established.
5.3. Preclinical safety data "variation of 18/03/13"	Tests performed *in vitro* or in animals revealed no carcinogenic or mutagenic effect. In a toxicology study in juvenile animals, the administration of a dose of 30 mg/kg/day of fluoxetine hydrochloride to young "CD" rats aged 21-90 days led to irreversible testicular degeneration and necrosis, epididymal epithelial vacuolation, immaturity and inactivity of the female reproductive system, and to a reduction in fertility. Delayed sexual maturation appeared in the males (10 and 30 mg/kg/day) and the females (30 mg/kg/day). The significance of these data for human beings is unknown. Rats receiving a dose of 30 mg/kg also showed femur lengths shorter than those observed in the control group and, skeletal muscle degeneration, necrosis and regeneration. […]	Tests performed *in vitro* or in animals revealed no carcinogenic or mutagenic effect. *Studies in adult animals* In a reproduction study in rats over 2 generations, fluoxetine did not cause any adverse effects on the mating or fertility of the rats, was not teratogenic, and did not affect growth, development or the reproductive parameters of the offspring. The doses administered were approximately equivalent to 1.5, 3.9 and 9.7 mg fluoxetine/kg body weight. A reduction in the weight of the testes and hypospermatogenesis were observed in male mice receiving fluoxetine daily for 3 months at a dose approximately equivalent to 31 mg/kg. However, this dose exceeded the maximum tolerated dose (MTD), as significant signs of toxicity were seen. *Studies in juvenile animals* In a toxicology study in juvenile animals, the administration of a dose of 30 mg/kg/day of fluoxetine hydrochloride to young "CD" rats aged 21-90 days led to irreversible testicular degeneration and necrosis, epididymal epithelial vacuolation, immaturity and inactivity of the female reproductive system, and to a reduction in fertility. Delayed sexual maturation appeared in the males (10 and 30 mg/kg/day) and the females (30 mg/kg/day). The significance of these data for human beings is unknown. Rats receiving a dose of 30 mg/kg also showed femur lengths shorter than those observed in the control group s and skeletal muscle degeneration, necrosis and regeneration.. […]

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