PROZAC®

1. NAME OF THE MEDICINAL PRODUCT

PROZAC® 20mg hard capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 20mg of fluoxetine (as fluoxetine hydrochloride)

For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Hard capsules.

The capsules are green and yellow printed 'Lilly 3105'.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Depression: Prozac is indicated for the treatment of the symptoms of depressive illness, with or without associated anxiety symptoms.

Obsessive-compulsive disorder

Pre-menstrual Dysphoric Disorder (PMDD): Prozac is indicated for the treatment of pre-menstrual dysphoric disorder.
Diagnosis of PMDD: The essential diagnostic features of PMDD are clear and established cyclicity (occurring during the last week of the luteal phase in most menstrual cycles) of symptoms such as depressed mood, anxiety, affective liability, accompany by impairment in social and/or occupational function and physical symptoms (such as breast tenderness or swelling, headaches, joint or muscle pain, a sensation of bloating, weight gain) – all of which must be severe. This syndrome should be distinguished from the commoner "pre-menstrual tension (distinguished from PMDD by milder symptoms and less impact on normal activities)" and from any co-existing psychiatric disorder.

4.2 Posology and method of administration

For oral administration to adults only.

Depression, with or without associated anxiety symptoms
Adults and the elderly: The recommended dose is 20mg daily. Dosage 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, the dose may be increased gradually up to a maximum of 60 mg (see section 5.1). 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, the dose may be increased gradually up to a maximum of 60 mg.

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 systematic 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. Long-term efficacy (more than 24 weeks) has not been demonstrated in OCD.

Pre-menstrual Dysphoric Disorder (PMDD)
The recommended dose of fluoxetine for the treatment of PMDD is 20 mg/day given continuously (every day of the menstrual cycle) or intermittently (defined as starting a daily dose 14 days prior to the anticipated onset of menstruation through the first full day of menses and repeating with each new cycle).

All indications: The recommended dose may be increased or decreased. Doses above 80 mg/day have not been systematically evaluated.

Elderly patients
Caution is recommended when increasing the dose, and the daily dose should generally not exceed 40mg. Maximum recommended dose is 60 mg/day.

Hepatic impairment
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), or in patients where concomitant medication has the potential for interaction with PROZAC (see section 4.5).

Withdrawal symptoms seen on discontinuation of PROZAC: Abrupt discontinuation 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 section 4.4 and 4.8). If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, then resuming the previously prescribed dose may be considered. Subsequently, the physician may continue decreasing the dose, but at a more gradual rate.

Method of administration
For oral administration

Fluoxetine may be administered as a single or divided dose, during or between meals.

When dosing is stopped, active drug substances will persist in the body for weeks. This should be borne in mind when starting or stopping treatment.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Fluoxetine is contra-indicated in combination with irreversible, non-selective monoamine oxidase inhibitors (e.g. iproniazid) (see sections 4.4 and 4.5).

Fluoxetine is contra-indicated in combination with metoprolol used in cardiac failure (see section 4.5).

4.4 Special warnings and precautions for use

Suicide/suicidal thoughts or clinical worsening
Depression is associated with an increased risk of suicidal thoughts, self-harm and suicide (suicide-related events). This risk persists until significant remission occurs. As improvement may occur during the first few weeks or more of treatment, patients should be closely monitored until such improvement occurs. It is general clinical experience that the risk of suicide may increase in the early stages of recovery.

Other psychiatric conditions for which PROZAC is prescribed can also be associated with an increased risk of suicide-related events. In addition, these conditions may be co-morbid with major depressive disorder. The same precautions observed when treating patients with major depressive disorder should therefore be observed when treating patients with other psychiatric disorders.

Patients with a history of suicide-related events, those exhibiting a significant degree of suicidal ideation prior to commencement of treatment are known to be at greater risk of suicidal thoughts or suicide attempts, and should receive careful monitoring during treatment. A meta-analysis of placebo-controlled clinical trials of antidepressants drugs in adult patients with psychiatric disorders showed an increased risk of suicidal behavior with antidepressants compared to placebo in patients less than 25 years old.

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 caregivers of patients) should be alerted about the need to monitor for any clinical worsening, suicidal behavior or thoughts and unusual changes in behavior and to seek medical advice immediately if these symptoms present.

Suicidality in Children and Adolescents
Antidepressants increase the risk of suicidal thinking and behavior (suicidality) in children and adolescents with major depressive disorder (MDD) and other psychiatric disorders. Anyone considering the use of an antidepressant in a child or adolescent for any clinical use must balance the risk of increased suicidality with the clinical need. Patients who are started on therapy should be observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised to closely observe the patient and to communicate with the prescriber.

Cardiovascular Effects
Cases of QT interval prolongation and ventricular arrhythmia including torsades de pointes have been reported during the post-marketing period (see sections 4.5, 4.8 and 4.9).

Fluoxetine should be used with caution in patients with conditions such as congenital long QT syndrome, a family history of QT prolongation or other clinical conditions that predispose to arrhythmias (e.g. hypokalemia, hypomagnesemia, bradycardia, acute myocardial infarction or uncompensated heart failure) or increased exposure to fluoxetine (e.g. hepatic impairment), or concomitant use with medicinal products known to induce QT prolongation and/or torsade de pointes (see section 4.5).

If patients with stable cardiac disease are treated, an ECG review should be considered before treatment is started.

If signs of cardiac arrhythmia occur during treatment with fluoxetine, the treatment should be withdrawn and an ECG should be performed.

Irreversible, non-selective monoamine oxidase inhibitors (e.g. iproniazid)
Some cases of serious and sometimes fatal reactions have been reported in patients receiving an SSRI in combination with an irreversible, non-selective monoamine oxidase inhibitor (MAOI).

These cases presented with features resembling serotonin syndrome (which may be confounded with (or diagnosed as) neuroleptic malignant syndrome). Cyproheptadine or dantrolene may benefit patients experiencing such reactions. Symptoms of a drug interaction with a MAOI include: hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, mental status changes that include confusion, irritability and extreme agitation progressing to delirium and coma.

Therefore, fluoxetine is contra-indicated in combination with an irreversible, non-selective MAOI (see section 4.3). Because of the two weeks-lasting effect of the latter, treatment of fluoxetine should only be started 2 weeks after discontinuation of an irreversible, non-selective MAOI. Similarly, at least 5 weeks should elapse after discontinuing fluoxetine treatment before starting an irreversible, non-selective MAOI.

Serotonin syndrome or neuroleptic malignant syndrome-like events
On rare occasions development of a serotonin syndrome or neuroleptic malignant syndrome-like events have been reported in association with treatment of fluoxetine, particularly when given in combination with other serotonergic (among others L-tryptophan) and/or neuroleptic drugs (see section 4.5). As these syndromes may result in potentially life-threatening conditions, treatment with fluoxetine should be discontinued if such events (characterized by clusters of symptoms such as hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, mental status changes including confusion, irritability, extreme agitation progressing to delirium and coma) occur and supportive symptomatic treatment should be initiated.

Mania
Antidepressants should be used with caution in patients with a history of mania/hypomania. As with all antidepressants, fluoxetine should be discontinued in any patient entering a manic phase.

Haemorrhage
There have been reports of cutaneous bleeding abnormalities such as ecchymosis and purpura with SSRI's. Ecchymosis has been reported as an infrequent event during treatment with fluoxetine. SSRIs/SNRIs may increase the risk of postpartum haemorrhage (see sections 4.6, 4.8). Other haemorrhagic manifestations (eg, gynaecological haemorrhages, gastrointestinal bleedings, and other cutaneous or mucous bleedings) have been reported rarely. Caution is advised in patients taking SSRIs, particularly in concomitant use with oral anticoagulants, drugs known to affect platelet function (eg, atypical antipsychotics such as clozapine, phenothiazines, most TCAs, aspirin, NSAIDs), or other drugs that may increase risk of bleeding as well as in patients with a history of bleeding disorders (see section 4.5).

Seizures
Seizures are a potential risk with antidepressant drugs. Therefore, as with other antidepressants, fluoxetine should be introduced cautiously in patients who have a history of

seizures. Treatment should be discontinued in any patient who develops seizures or where there is an increase in seizure frequency. Fluoxetine should be avoided in patients with unstable seizure disorders/epilepsy and patients with controlled epilepsy should be carefully monitored (see section 4.5).

Electroconvulsive Therapy (ECT)
There have been rare reports of prolonged seizures in patients on fluoxetine receiving ECT treatment, therefore caution is advisable.

Tamoxifen
Fluoxetine, a potent inhibitor of CYP2D6, may lead to reduced concentrations of endoxifen, one of the most important active metabolites of tamoxifen. Therefore, fluoxetine should whenever possible be avoided during tamoxifen treatment (see section 4.5)

Akathisia/psychomotor restlessness
The use of fluoxetine has been associated with the development of akathisia, characterized by a subjectively unpleasant or distressing restlessness and need to move often accompanied by an inability to sit or stand still. This is most likely to occur within the first few weeks of treatment. In patients who develop these symptoms, increasing the dose may be detrimental.

Diabetes
In patients with diabetes, treatment with an SSRI may alter glycaemic control. Hypoglycaemia has occurred during therapy with fluoxetine and hyperglycaemia has developed following discontinuation. Insulin and/or oral hypoglycaemic dosage may need to be adjusted.

Hepatic/Renal Function
Fluoxetine is extensively metabolized by the liver and excreted by the kidneys. A lower dose, e.g., alternate day dosing, is recommended in patients with significant hepatic dysfunction. When given fluoxetine 20 mg/day for 2 months, patients with severe renal failure (GFR <10 ml/min) requiring dialysis showed no difference in plasma levels of fluoxetine or norfluoxetine compared to controls with normal renal function.

Rash and allergic reactions
Rash, anaphylactoid events and progressive systemic events, sometimes serious (involving skin, kidney, liver or lung) have been reported. Upon the appearance of rash or other allergic phenomena for which an alternative aetiology cannot be identified, fluoxetine should be discontinued.

Weight loss
Weight loss may occur in patients taking fluoxetine, but it is usually proportional to baseline body weight.

Withdrawal symptoms seen on discontinuation of SSRI treatment
Withdrawal symptoms when treatment is discontinued are common, particularly if discontinuation is abrupt (see section 4.8). In clinical trials, adverse events see on treatment discontinuation occurred in approximately 60% of patients in both the fluoxetine and placebo groups. Of the adverse events, 17% in the fluoxetine group and 12 % in the placebo group were severe in nature.

The risk of withdrawal symptoms may be dependent on several factors, including the duration and dose of therapy and the rate of dose reduction. Dizziness, sensory disturbances (including paraesthesia), sleep disturbances (including insomnia and intense dreams), asthenia, agitation or anxiety, nausea, and /or vomiting, tremor, and headache are the most commonly reported reactions. Generally, these symptoms are mild to moderate; however, in some patients they

may be severe in intensity. They usually occur within the first few days of discontinuing treatment. Generally, these symptoms are self-limiting and usually resolve with 2 weeks, though in some individuals they may be prolonged (2-3 months or more). It is therefore advised that PROZAC should be gradually tapered when discontinuing treatment over a period of at least one to two weeks, according to the patient's need (see *Withdrawal symptoms seen on discontinuation of PROZAC*, section 4.2)

Mydriasis
Mydriasis has been reported in association with fluoxetine; therefore, caution should be used when prescribing fluoxetine in patients with raised intraocular pressure or those at risk of acute narrow-angle glaucoma.

Sexual dysfunction
Selective serotonin reuptake inhibitors (SSRI) may cause symptoms of sexual dysfunction (see section 4.8). There have been reports of long-lasting sexual dysfunction where the symptoms have continued despite discontinuation of SSRIs.

4.5 Interaction with other medicinal products and other forms of interaction

Half-life: The long elimination half-lives of both fluoxetine and norfluoxetine should be borne in mind (see section 5.2) when considering pharmacodynamic or pharmacokinetic drug interactions (e.g. when switching from fluoxetine to other antidepressants).

Contra-indicated combinations
Irreversible, non-selective monoamine oxidase inhibitors (e.g. iproniazid): Some cases of serious and sometimes fatal reactions have been reported in patients receiving an SSRI in combination with an irreversible, non-selective monoamine oxidase inhibitor (MAOI).

These cases presented with features resembling serotonin syndrome (which may be confounded with [or diagnosed as] neuroleptic malignant syndrome). Cyproheptadine or dantrolene may benefit patients experiencing such reactions. Symptoms of a drug interaction with a MAOI include: hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, mental status changes that include confusion, irritability and extreme agitation progressing to delirium and coma.

Therefore, fluoxetine is contra-indicated in combination with an irreversible, non-selective MAOI (see section 4.3). Because of the two weeks-lasting effect of the latter, treatment of fluoxetine should only be started 2 weeks after discontinuation of an irreversible, non-selective MAOI. Similarly, at least 5 weeks should elapse after discontinuing fluoxetine treatment before starting an irreversible, non-selective MAOI.

Metroprolol used in cardiac failure: risk of metoprolol adverse events, including excessive bradycardia, may be increased because of an inhibition of its metabolism by fluoxetine (see section 4.3).

Not recommended combinations
Tamoxifen: Pharmacokinetic interaction between CYP2D6 inhibitors and tamoxifen, showing a 65-75 % reduction in plasma levels of one of the more active forms of the tamoxifen, i.e. endoxifen, has been reported in the literature. Reduced efficacy of tamoxifen has been reported with concomitant usage of some SSRI antidepressants in some studies. As a reduced effect of tamoxifen cannot be excluded, co-administration with potent CYP2D6 inhibitors (including fluoxetine) should whenever possible be avoided (see section 4.4).

Alcohol: In formal testing, fluoxetine did not raise blood alcohol levels or enhance the effects of alcohol. However, the combination of SSRI treatment and alcohol is not advisable.

MAOI-A including linezolid and methylothioninium chloride (methylene blue): Risk of serotonin syndrome including diarrhea, tachycardia, sweating, tremor, confusion or coma. If the concomitant use of these active substances with fluoxetine cannot be avoided, close clinical monitoring should be undertaken and the concomitant agents should be initiated at the lower recommended doses (see section 4.4).

Mequitazine: risk of mequitazine adverse events (such as QT prolongation) may be increased because of an inhibition of its metabolism by fluoxetine.

Combinations requiring caution
Phenytoin: Changes in blood levels have been observed when combined with fluoxetine. In some cases manifestations of toxicity have occurred. Consideration should be given to using conservative titration schedules of the concomitant drug and to monitoring clinical status.

Serotoninergic drugs (lithium, tramadol, triptans, tryptophan, selegiline (MAOI-B), St. John's Wort (Hypericum perforatum)): There have been reports of mild serotonin syndrome when SSRIs where given with drugs also having a serotoninergic effect. Therefore, the concomitant use of fluoxetine with these drugs should be undertaken with caution, with closer and more frequent clinical monitoring (see section 4.4).

QT interval prolongation: Pharmacokinetic and pharmacodynamic studies between fluoxetine and other medicinal products that prolong the QT interval have not been performed. An additive effect of fluoxetine and these medicinal products cannot be excluded. Therefore, co-administration of fluoxetine with medicinal products that prolong the QT interval, such as Class IA and III antiarrhythmics, antipsychotics (e.g. phenothiazine derivatives, pimozide, haloperidol), tricyclic antidepressants, certain antimicrobial agents (e.g. sparfloxacin, moxifloxacin, erythromycin IV, pentamidine), anti-malaria treatment particularly halofantrine, certain antihistamines (astemizole, mizolastine), should be used with caution (see sections 4.4, 4.8 and 4.9).

Drugs affecting haemostasis (oral anticoagulants, whatever their mechanism, platelets antiaggregants including aspirin and NSAIDs): risk of increased bleeding. Clinical monitoring, and more frequent monitoring of INR with oral anticoagulants, should be made. A dose adjustments during the fluoxetine treatment and after its discontinuation may be suitable (see section 4.4 and 4.8).

Cyproheptadine: There are individual case reports of reduced antidepressant activity of fluoxetine when used in combination with cyproheptadine.

Drugs inducing hyponatremia: Hyponatremia is an undesirable effect of fluoxetine. Use in combination with other agents associated with hyponatremia (e.g. diuretics, desmopressin, carbamazepine and oxcarbazepine) may lead to an increased risk (see section 4.8).

Drugs lowering the epileptogenic threshold: Seizures are an undesirable effect of fluoxetine. Use in combination with other agents which may lower the seizure threshold (for example, TCAs, other SSRIs, phenothiazines, butyrophenones, mefloquine, chloroquine, bupropion, tramadol) may lead to an increased risk.

Other drugs metabolized by CYP2D6: Fluoxetine is a strong inhibitor of CYP2D6 enzyme, therefore concomitant therapy with drugs also metabolized by this enzyme system may lead to drug interactions, notable those having a narrow therapeutic index (such as flecainide, propafenone and nebivolol) and those that are titrated, but also with atomoxetine, carbamazepine, tricyclic antidepressants and risperidone. They should be initiated at or adjusted to the low end of their dose range. This may also apply if fluoxetine has been taken in the previous 5 weeks.

4.6 Fertility, pregnancy and lactation

Pregnancy
Some epidemiological studies suggest an increased risk of cardiovascular defects associated with the use of fluoxetine during the first trimester. The mechanism is unknown. Overall the data suggest that the risk of having an infant with a cardiovascular defect following maternal fluoxetine exposure is in the region of 2/100 compared with an expected rate for such defects of approximately 1/100 in the general population.

Epidemiological data have suggested that the use of SSRIs in pregnancy, particular in late pregnancy, may increase the risk of persistent pulmonary hypertension in the newborn (PPHN). The observed risk was approximately 5 cases per 1000 pregnancies. In the general population 1 to 2 cases of PPHN per 1000 pregnancies occur.

Observational data indicate an increased risk (less than 2-fold) of postpartum haemorrhage following SSRI/SNRI exposure within the month prior to birth (see sections 4.4, 4.8).

Fluoxetine should not be used during pregnancy unless the clinical condition of the woman requires treatment with fluoxetine and justifies the potential risk to the foetus. Abrupt discontinuation of therapy should be avoided during pregnancy (see section 4.2 “Posology and method of administration”). If fluoxetine is used during pregnancy, caution should be exercised, especially during late pregnancy or just prior to the onset of labour since some other effects have been reported in neonates: irritability, tremor, hypotonia, persistent crying, difficulty in sucking or in sleeping. These symptoms may indicate either serotonergic effects or a withdrawal syndrome. The time to occur and the duration of these symptoms may be related 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 known to be excreted in human breast milk. Adverse events have been reported in breastfeeding infants. If treatment with fluoxetine is considered necessary, discontinuation of breastfeeding should be considered; however, if breastfeeding 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 SSRI’s have shown that an effect on sperm quality is reversible.

Impact on human fertility has not been observed so far.

4.7 Effects on ability to drive and use machines

Prozac has no or negligible influence on the ability to drive and use machines. Although fluoxetine has been shown not to affect psychomotor performance in healthy volunteers, any psychoactive drug may impair judgement or skills. Patients should be advised to avoid driving a car or operating hazardous machinery until they are reasonably certain that their performance is not affected.

4.8 Undesirable effects

a. Summary of the safety profile

The most commonly reported adverse reactions in patients treated with fluoxetine were headache, nausea, insomnia, fatigue and diarrhoea. Undesirable effects may decrease in intensity and frequency with continued treatment and do not generally lead to cessation of therapy.

b. Tabulated list of adverse reactions

The table below gives the adverse reactions observed with fluoxetine treatment in adult and paediatric populations. Some of these adverse reactions are in common with other SSRIs.

The following frequencies have been calculated from clinical trials in adults (n=9297) and from spontaneous reporting.

Frequency estimate: Very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), not known (cannot be estimated from the available data).

Very Common	Common	Uncommon	Rare	Not Known
Blood and lymphatic system disorders				
			Thrombocytopenia Neutropenia Leucopenia	
Immune system disorders				
			Anaphylactic reaction Serum sickness	
Endocrine disorders				
			Inappropriate antidiuretic hormone secretion	
Metabolism and nutrition disorders				
	Decreased appetite[1]		Hyponatraemia	
Psychiatric disorders				
Insomnia[2]	Anxiety Nervousness Restlessness Tension Libido decreased[3] Sleep disorder Abnormal dreams[4]	Depersonalisation Elevated mood Euphoric mood Thinking abnormal Orgasm abnormal[5] Bruxism Suicidal thoughts and behaviour[6]	Hypomania Mania Hallucinations Agitation Panic attacks Confusion Dysphemia Aggression	
Nervous system disorders				
Headache	Disturbance in	Psychomotor	Convulsion	

	attention Dizziness Dysgeusia Lethargy Somnolence[7] Tremor	hyperactivity Dyskinesia Ataxia Balance disorder Myoclonus Memory impairment	Akathisia Buccoglossal syndrome Serotonin syndrome	
Eye disorders				
	Vision blurred	Mydriasis		
Ear and labyrinth disorders				
		Tinnitus		
Cardiac disorders				
	Palpitations Electrocardiogram QT prolonged (QTcF ≥450 msec)[8]		Ventricular arrhythmia including torsades de pointes	
Vascular disorders				
	Flushing[9]	Hypotension	Vasculitis Vasodilatation	
Respiratory, thoracic and mediastinal disorders				
	Yawning	Dyspnoea Epistaxis	Pharyngitis Pulmonary events (inflammatory processes of varying histopathology and/or fibrosis)[10]	
Gastrointestinal disorders				
Diarrhoea Nausea	Vomiting Dyspepsia Dry mouth	Dysphagia Gastrointestinal haemorrhage[11]	Oesophageal pain	
Hepato-biliary disorders				
			Idiosyncratic hepatitis	
Skin and subcutaneous tissue disorders				
	Rash[12] Urticaria Pruritus Hyperhidrosis	Alopecia Increased tendency to bruise Cold sweat	Angioedema Ecchymosis Photosensitivity reaction Purpura Erythema multiforme Stevens-Johnson	

			syndrome Toxic Epidermal Necrolysis (Lyell Syndrome)	
Musculoskeletal, and connective tissue disorders				
	Arthralgia	Muscle twitching	Myalgia	
Renal and urinary disorders				
	Frequent urination[13]	Dysuria	Urinary retention Micturition disorder	
Reproductive system and breast disorders				
	Gynaecological bleeding[14] Erectile dysfunction Ejaculation disorder[15]	Sexual dysfunction[16]	Galactorrhoea Hyperprolactinemia Priapism	Postpartum haemorrhage[17]
General disorders and administration site conditions				
Fatigue[18]	Feeling jittery Chills	Malaise Feeling abnormal Feeling cold Feeling hot	Mucosal haemorrhage	
Investigations				
	Weight decreased	Transaminases increased Gamma-glutamyltransferase increased		

[1] Includes anorexia
[2] Includes early morning awakening, initial insomnia, middle insomnia
[3] Includes loss of libido
[4] Includes nightmares
[5] Includes anorgasmia
[6] Includes completed suicide, depression suicidal, intentional self-injury, self-injurious ideation, suicidal behavior, suicidal ideation, suicide attempt, morbid thoughts, self-injurious behavior. These symptoms may be due to underlying disease
[7] Includes hypersomnia, sedation
[8] Based on ECG measurements from clinical trials
[9] Includes hot flush
[10] Includes atelectasis, interstitial lung disease, pneumonitis
[11] Includes most frequently gingival bleeding, haematemesis, haematochezia, rectal haemorrhage, diarrhea haemorrhagic, melaena, and gastric ulcerhaemorrhage
[12] Includes erythema, exfoliative rash, heat rash, rash, rash erythematous, rash follicular, rash generalized, rash macular, rash macular-papular, rash morbilliform, rash papular, rash pruritic, rash vesicular, umbilical erythema rash
[13] Includes pollakiuria

[14] Includes cervix haemorrhage, uterine dysfunction, uterine bleeding, genital haemorrhage, menometrorhagia, menorrhagia, metrorrhagia, polymenorrhea, postmenopausal haemorrhage, uterine haemorrhage, vaginal haemorrhage
[15] Includes ejaculation failure, ejaculation dysfunction, premature ejaculation, ejaculation delayed, retrograde ejaculation
[16] Occasionally persisting after treatment discontinuation
[17] This event has been reported for the therapeutic class of SSRIs/SNRIs (see sections 4.4, 4.6).
[18] Includes asthenia

c. Description of selected adverse reactions
Suicide/suicidal thoughts or clinical worsening: Cases of suicidal ideation and suicidal behavior have been reported during fluoxetine therapy or early after treatment discontinuation (see section 4.4).
Bone fractures: Epidemiological studies, mainly conducted in patients 50 years of age and older, show an increased risk of bone fractures in patients receiving SSRIs and TCAs. The mechanism leading to the risk is unknown.

Withdrawal symptoms seen on discontinuation of fluoxetine treatments: Discontinuation of fluoxetine commonly leads to withdrawal symptoms. Dizziness, sensory disturbances (including paraesthesia), sleep disturbances (including insomnia and intense dreams), asthenia, agitation or anxiety, nausea and/or vomiting, tremor and headache are the most commonly reported reactions. Generally these events are mild to moderate and are self-limiting, however, in some patients they may be severe and/or prolonged (see section 4.4). It is therefore advised that when Prozac treatment is no longer required, gradual discontinuation by dose tapering should be carried out (see sections 4.2 and 4.4).

4.9 Overdose

Symptoms
Cases of overdose of fluoxetine alone usually have a mild course. Symptoms of overdose have included nausea, vomiting, seizures, cardiovascular dysfunction ranging from asymptomatic arrhythmias (including nodal rhythm and ventricular arrhythmias) or ECG changes indicative of QTc prolongation to cardiac arrest (including very rare cases of Torsades de Pointes), pulmonary dysfunction, and signs of altered CNS status ranging from excitation to coma. Fatality attributed to overdose of fluoxetine alone has been extremely rare.

Management
Cardiac and vital signs monitoring are recommended, along with general symptomatic and supportive measures. No specific antidote is known.

Forced diuresis, dialysis, haemoperfusion, and exchange transfusion are unlikely to be of benefit. Activated charcoal, which may be used with sorbitol, may be as or more effective than emesis or lavage. In managing overdosage, consider the possibility of multiple drug involvement. An extended time for close medical observation may be needed in patients who have taken excessive quantities of a tricyclic antidepressant if they are also taking, or have recently taken, fluoxetine.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Selective serotonin reuptake inhibitors. ATC code: N06A B03.

Mechanism of action
Fluoxetine is a selective inhibitor of serotonin reuptake, and this probably accounts for the mechanism of action. Fluoxetine has practically no affinity to other receptors such as α_1-, α_2-,

and β-adrenergic; serotonergic; dopaminergic; histaminergic$_1$; muscarinic; and GABA receptors.

Clinical efficacy and safety
Major depressive episodes: Clinical trials in patients with major depressive episodes have been conducted versus placebo and active controls. PROZAC has been shown to be significantly more effective than placebo, as measured by the Hamilton Depression Rating Scale (HAM-D). In these studies, PROZAC produced a significantly higher rate of response (defined by 50% decrease in the HAM-D score) and remission compared to placebo.

Dose response: In the fixed-dose studies of patients with major depression there is a flat dose response curve, providing no suggestion of advantage in terms of efficacy for using higher than the recommended doses. However, it is clinical experience that uptitrating might be beneficial for some patients.

Obsessive-compulsive disorder: In short-term trials (under 24 weeks), fluoxetine was shown to be significantly more effective than placebo. There was a therapeutic effect at 20mg/day, but higher doses (40 or 60mg/day) showed a higher response rate. In long-term studies (three short-term studies extension phase and a relapse prevention study), efficacy has not been shown.

*Pre-Menstrual Dysphoric Disorde*r: Two placebo-controlled studies were conducted in patients meeting Pre-Menstrual Dysphoric Disorder (PMDD) diagnostic criteria according to DSM-IV. Patients were included if they had symptoms of sufficient severity to impair social and occupational function and relationships with others. Patients using oral contraceptives were excluded. In the first study of continuous 20 mg daily dosing for 6 cycles, improvement was observed in the primary efficacy parameter (irritability, anxiety and dysphoria). In the second study, with intermittent luteal phase dosing (20 mg daily for 14 days) for 3 cycles, improvement was observed in the primary efficacy parameter (Daily Record of Severity of Problems score). However, definitive conclusions on efficacy and duration of treatment cannot be drawn from these studies.

5.2 Pharmacokinetic properties

Absorption
Fluoxetine is well absorbed from the gastro-intestinal tract after oral administration. The bioavailability is not affected by food intake.

Distribution
Fluoxetine is extensively bound to plasma proteins (about 95%) and it is widely distributed (Volume of Distribution: 20-40 L/kg). Steady-state plasma concentrations are achieved after dosing for several weeks. Steady-state concentrations after prolonged dosing are similar to concentrations seen at 4 to 5 weeks.

Biotransformation
Fluoxetine has non-linear pharmacokinetic profile with first-pass liver effect. Maximum plasma concentration is generally achieved 6 to 8 hours after administration. Fluoxetine is extensively metabolized by the polymorphic enzyme CYP2D6. Fluoxetine is primarily metabolized by the liver to the active metabolite norfluoxetine (desmethylfluoxetine), by desmethylation.

Elimination
The elimination half-life of fluoxetine is 4 to 6 days and for norfluoxetine 4 to 16 days. These long half-lives are responsible for persistence of the drug for 5-6 weeks after discontinuation. Excretion is mainly (about 60%) via the kidney. Fluoxetine is secreted into breast milk.

Special populations

Elderly: Kinetic parameters are not altered in healthy elderly when compared to younger subjects.

Hepatic insufficiency: In case of hepatic insufficiency (alcoholic cirrhosis), fluoxetine and norfluoxetine half-lives are increased to 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 complete (anuria) renal insufficiency, kinetic parameters have not been altered when compared to healthy volunteers. However, after repeated administration, an increase in steady-state plateau of plasma concentrations may be observed.

5.3 Preclinical safety data

There is no evidence of carcinogenicity or mutagenicity from *in vitro* or animal studies.

Adult animal studies
In a 2-generation rat reproduction study, fluoxetine did not produce adverse effects on the mating or fertility of rats, was not teratogenic, and did not affect growth, development, or reproductive parameters of the offspring.

The concentrations in the diet provided doses approximately equivalent to 1.5, 3.9, and 9.7 mg fluoxetine/kg body weight.

Male mice treated daily for 3 months with fluoxetine in the diet at a dose approximately equivalent to 31 mg/kg showed a decrease in testis weight and hypospermatogenesis. However, this dose level exceeded the maximum-tolerated dose (MTD) as significant signs of toxicity were seen.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipient(s)

The capsules contain:
Starch flowable
Dimeticone

Capsule components:
Patent blue V
Yellow iron oxide
Titanium dioxide
Gelatin
Pharmaceutical grade edible printing ink

6.2 Incompatibilities

Not applicable.

6.3 Shelf-life

Please refer to the expiry date on the product labels.

6.4 Special precautions for storage

Please refer to the recommended storage condition on the product labels.

6.5 Nature and contents of container

Prozac capsules are available in blister strip packs in cartons of 28 capsules per carton. Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirement

7. MANUFACTURER

Patheon France, 38300 Bourgoin-Jallieu.

8. DATE OF REVISION

23 Feb 2021