NEW ZEALAND DATA SHEET

FLUOX

1. Product Name

FLUOX, fluoxetine hydrochloride, capsules.

FLUOX, fluoxetine hydrochloride, dispersible tablets.

2. Qualitative and Quantitative Composition

Capsules

Each capsule contains fluoxetine hydrochloride equivalent to 20 mg fluoxetine.

Excipients with known effect: Lactose monohydrate and colloidal anhydrous silica, maize starch and gelatin.

Allergen Declaration: contains sulfites and sugars as lactose.

Each 20 mg capsule contains 140 mg of lactose monohydrate, 1 mg of colloidal anhydrous silica, 25 mg of maize starch and 47 mg of gelatin.

For the full list of excipients, see section 6.1.

Dispersible tablets

Each dispersible tablet contains fluoxetine hydrochloride equivalent to 20 mg fluoxetine.

Excipients with known effect: Saccharin sodium, microcrystalline cellulose, maize starch, crospovidone and peppermint powder.

Allergen Declaration: contains saccharin and sulfites.

Each 20 mg dispersible tablet contains 8 mg of saccharin sodium, 103 mg of microcrystalline cellulose, 20 mg of maize starch, 30 mg of crospovidone and 30 mg peppermint powder.

For the full list of excipients, see section 6.1.

3. Pharmaceutical Form

FLUOX 20 mg capsules are presented as size 3, hard gelatin capsules with a light green opaque body and a purple opaque cap, printed in black ink "FL20" on the body and "α" on the cap.

FLUOX 20 mg dispersible tablets are 12.6 x 6 mm oval, normal convex, white tablets, debossed "FL" breakline "20" on one side and "G" on the other. The tablet can be divided into equal doses.

4. Clinical Particulars

4.1 Therapeutic indications

In adults 18 years of age and over:

- Depression and its associated anxiety
- Bulimia nervosa
- Obsessive-Compulsive disorder
- Premenstrual dysphoric disorder - a severe form of PMS

Diagnosis of PMDD: The essential features of PMDD are clear and established cyclicity of symptoms (occurring during the last week of the luteal phase in most menstrual cycles) such as depressed mood, anxiety, affective lability, and physical symptoms such as breast tenderness or swelling, headaches, joint or muscle pain, bloating, and weight gain. PMDD is a severe clinical entity and is distinguished from the broader premenstrual syndrome by the intensity of its symptoms (particularly mood symptoms) and the extent to which it interferes with social and/or occupational function.

4.2 Dose and method of administration

Dose

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

Depression:	20 mg per day is the recommended initial dose.
Bulimia nervosa:	60 mg per day is the recommended dose.
Obsessive-Compulsive disorder:	20 mg to 60 mg per day is the recommended dose.
Premenstrual dysphoric disorder:	20 mg per day is recommended continuously throughout the menstrual cycle. Initial treatment should be limited to six months, after which patients should be reassessed regarding the benefit of continued therapy***.***

Special populations

A lower or less frequent dose should be considered in patients with hepatic impairment, with concurrent diseases, or who are taking multiple medications.

Age

There are no data to suggest that alternative dosing is required on the basis of age alone.

Paediatric

While clinical studies have been conducted in children and adolescents, the use of fluoxetine is not recommended in this population (see section 4.4, section 4.8 and section 5.3).

Method of administration

FLUOX may be administered with or without food.

4.3 Contraindications

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

Fluoxetine should not be used in combination with a monoamine oxidase inhibitor (MAOI) or within a minimum of 14 days of discontinuing treatment with a MAOI. At least five weeks should elapse between discontinuation of fluoxetine and initiation of therapy with a MAOI. If fluoxetine has been prescribed chronically and/or at a high dose, a longer interval should be considered. Serious and

fatal cases of serotonin syndrome (which may resemble and be diagnosed as neuroleptic malignant syndrome) have been reported in patients treated with fluoxetine and a MAOI in close temporal proximity.

4.4 Special warnings and precautions for use

Clinical worsening and suicide risk

The risk of suicide attempt is inherent in depression and other psychiatric disorders and may persist until significant remission occurs. As with other drugs with similar pharmacological action (antidepressants), isolated cases of suicidal ideation and suicidal behaviours have been reported during fluoxetine therapy or early after treatment discontinuation. This risk must be considered in all depressed patients.

Although a causal role for fluoxetine in inducing such events has not been established, some analyses from pooled studies of antidepressants in psychiatric disorders found an increased risk for suicidal ideation and/or suicidal behaviours in paediatric and young adult (< 25 years of age) patients compared to placebo. Patients with depression may experience worsening of their depressive symptoms and/or the emergence of suicidal ideation and behaviours (suicidality) whether or not they are taking antidepressant medications, and this risk may persist until significant remission occurs. As improvement may not occur during the first few weeks or more of treatment, patients should be closely monitored for clinical worsening and suicidality, especially at the beginning of a course of treatment, or at the time of dose changes, either increases or decreases. Consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medication, in patients whose depression is persistently worse or whose emergent suicidality is severe, abrupt in onset, or was not part of the patient's presenting symptoms. Patients (and caregivers of patients) should be alerted about the need to closely monitor for any worsening of their condition and/or the emergence of suicidal ideation/ behaviour or thoughts of harming themselves and to seek medical advice immediately if these symptoms present. Physicians should encourage patients of all ages to report any distressing thoughts or feelings at any time. Patients with co-morbid depression associated with other psychiatric disorders being treated with antidepressants should be similarly observed for clinical worsening and suicidality.

Pooled analyses of 24 short-term (4 to 16 weeks), placebo-controlled trials of nine antidepressant medicines [selective serotonin reuptake inhibitors (SSRIs) and others] in 4400 children and adolescents with major depressive disorder (16 trials), obsessive compulsive disorder (4 trials), or other psychiatric disorders (4 trials) have revealed a greater risk of adverse events representing suicidal behaviour or thinking (suicidality) during the first few months of treatment in those receiving antidepressants. The average risk of such events in patients treated with an antidepressant was 4%, compared with 2% of patients given placebo. There was considerable variation in risk among the antidepressants, but there was a tendency towards an increase for almost all antidepressants studied. The risk of suicidality was most consistently observed in the major depressive disorder trials, but there were signals of risk arising from trials in other psychiatric indications (obsessive compulsive disorder and social anxiety disorder) as well. No suicides occurred in these trials. It is unknown whether the suicidality risk in children and adolescent patients extends to use beyond several months. The nine antidepressant medicines in the pooled analyses included five SSRIs (citalopram, fluoxetine, fluvoxamine, paroxetine, sertraline) and four non-SSRIs (bupropion, mirtazapine, nefazodone, venlafaxine).

Symptoms of anxiety, agitation, panic attacks, insomnia, irritability, hostility (aggressiveness), impulsivity, akathisia (psychomotor restlessness), hypomania, and mania, have been reported in adults, adolescents and children being treated with antidepressants for major depressive disorder as well as for other indications, both psychiatric and non-psychiatric. Although a causal link between the emergence of such symptoms and either worsening of depression and/or emergence of suicidal impulses has not been established, there is concern that such symptoms may be precursors of emerging suicidality.

Families and caregivers of children and adolescents being treated with antidepressants for major depressive disorder or for any other condition (psychiatric or nonpsychiatric) should be informed

about the need to monitor these patients for the emergence of agitation, irritability, unusual changes in behaviour, and other symptoms described above, as well as the emergence of suicidality, and to report such symptoms to health care providers immediately. It is particularly important that monitoring be undertaken during the initial few months of antidepressant treatment or at times of dose increase or decrease.

Prescriptions for FLUOX should be written for the smallest quantity of medicine consistent with good patient management, in order to reduce the risk of overdose.

Cardiovascular effects

QT prolongation can occur with fluoxetine treatment. Cases of QTc prolongation and Torsades de Pointes (TdP) have been reported during the post-marketing use of fluoxetine. The majority of reports occurred in patients with other risk factors for QTc prolongation/TdP. Fluoxetine should be used with caution in patients with risk factors for QTc prolongation including, congenital long QT syndrome, age > 65 years, female sex, structural heart disease/LV dysfunction, medical conditions such as hepatic disease, use of medicines that inhibit the metabolism of fluoxetine, electrolyte imbalance (hypokalaemia and hypomagnesaemia should be corrected prior to treatment), and the concomitant use of other QT prolonging medicines (see section 4.5). Another factor associated with QTc prolongation is a family history of QTc prolongation.

In high risk patients (e.g. congenital long QT syndrome or multiple risk factors), an ECG should be performed prior to starting treatment, at steady state, after dose increases or after starting any potentially interacting medicine. Electrolytes should be monitored periodically.

An ECG should also be performed in all patients experiencing symptoms that could be indicative of an arrhythmia (e.g. dizziness, palpitations, syncope or new onset seizures).

Consideration should be given to stopping fluoxetine treatment or reducing the dose if the QTc interval is > 500 ms or increases by > 60 ms.

Rash

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

Mania and bipolar disorder

A major depressive episode may be the initial presentation of bipolar disorder. It is generally believed (though not established in controlled trials) that treating such an episode with any antidepressant alone may increase the likelihood of a mixed/manic episode in patients at risk for bipolar disorder. Prior to initiating treatment with an antidepressant, patients with depressive symptoms should be adequately screened to determine if they are at risk for bipolar disorder. It should be noted that fluoxetine is not approved for use in treating bipolar depression.

Seizures

As with other antidepressants, fluoxetine should be introduced cautiously in patients who have a history of seizures.

Hyponatraemia

Cases of hyponatraemia (some with serum sodium lower than 110 mmol/L) have been reported. The majority of these cases occurred in elderly patients and in patients treated with diuretics or otherwise volume-depleted.

Glycaemic control

In patients with diabetes, hypoglycaemia has occurred during therapy with fluoxetine and hyperglycaemia has developed following discontinuation. Insulin and/or oral hypoglycaemic dosage may need to be adjusted when fluoxetine therapy is initiated or discontinued.

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.

Abnormal bleeding

SSRIs and SNRIs, including fluoxetine, may increase the risk of bleeding events, including gastrointestinal bleeding (see section 4.8) and postpartum haemorrhage (see section 4.6). Therefore, caution is advised in patients taking fluoxetine concomitantly with anticoagulants and/or medicinal products known to affect platelet function (e.g., NSAIDs, aspirin) and in patients with known bleeding tendencies.

Withdrawal reactions

Discontinuation symptoms have been reported in association with selective serotonin reuptake inhibitors (SSRIs). Because of the long elimination half-life of fluoxetine, and its active metabolite norfluoxetine, plasma fluoxetine and norfluoxetine concentrations decrease gradually at the conclusion of therapy, which reduces greatly the likelihood of developing discontinuation symptoms and makes dosage tapering unnecessary in most patients. Common symptoms associated with withdrawal of SSRIs include dizziness, paraesthesia, headache, anxiety and nausea. Onset of symptoms can occur within a day of discontinuation but may be delayed, particularly in the case of fluoxetine, due to its long half-life. The majority of symptoms experienced on withdrawal of SSRIs are non serious, self-limiting and have varying durations. Fluoxetine has been only rarely associated with such symptoms.

Haemorrhage

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

Reversible cerebral Vasoconstriction syndrome (Thunderclap headache)

Reversible cerebral vasoconstriction syndrome (thunderclap headache) has been associated with serotonergic agents such as SSRIs or triptans.

Tamoxifen

Fluoxetine, a potent inhibitor of CYPIID6, 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, characterised 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.

Serotonin Syndrome

Development of serotonin syndrome or neuroleptic malignant syndrome-like events may occur in association with treatment with SSRIs, particularly when given in combination with MAOIs (see section 4.3) or other serotonergic and/or neuroleptic medicines. Examples of serotonergic medicines include opioids such as pethidine, tramadol and dextromethorphan.

Signs and symptoms of serotonin syndrome include rapid onset of neuromuscular excitation (hyperreflexia, incoordination, myoclonus, tremor), altered mental status (confusion, agitation, hypomania) and autonomic dysfunction (diaphoresis, diarrhoea, fever, shivering and rapidly fluctuating vital signs). Treatment with fluoxetine and/or the interacting medicine should be discontinued or reduced depending on severity of symptoms, if such events occur and supportive treatment should be initiated.

Alcohol

As with other psychotropic drugs patients should be advised to avoid alcohol use while taking fluoxetine.

Information for patients and families

Physicians are advised to discuss the following issues with patients for whom they prescribe fluoxetine:

- Because fluoxetine may impair judgement, thinking, or motor 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.
- Patients should be advised to inform their physician if they are taking or plan to take any prescription or over-the-counter medicines, or alcohol.
- Patients should be advised to inform their physician if they become pregnant or intend to become pregnant during therapy.
- Patients should be advised to notify their physician if they are breast feeding an infant.
- Patients should be advised to notify their physician if they develop a rash or hives.

The patient has the right to treatment meeting appropriate ethical and professional standards, and the patient needs to be fully informed with frank discussion of risk/benefit issues relating to the medicine's efficacy and safety when used in the treatment regimen proposed.

4.5 Interaction with other medicines and other forms of interaction

Monoamine oxidase inhibitors

See section 4.3.

Medicines metabolized by cytochrome P450IID6 isoenzyme

Because fluoxetine has the potential to inhibit the cytochrome P450IID6 isoenzyme, therapy with medications that are predominantly metabolised by the P450IID6 system and that have a relatively narrow therapeutic index should be initiated at the low end of the dose range if a patient is receiving fluoxetine concurrently or has taken it in the previous five weeks. If fluoxetine is added to the treatment range of a patient already receiving such a medicine, the need for decreased dose of the original medication should be considered.

CNS active medicines

Changes in the blood levels of phenytoin, carbamazepine, haloperidol, clozapine, diazepam, alprazolam, lithium, imipramine and desipramine, and in some cases, clinical manifestations of toxicity have been observed. Consideration should be given to using conservative titration schedules of the concomitant medicine and monitoring of clinical status.

Serotonergic drugs

Concomitant use of other drugs with serotonergic activity (e.g. SNRIs, SSRIs, triptans or opioids such as pethidine, dextromethorphan, tramadol) may result in serotonin syndrome (see section 4.4).

Lithium and tryptophan

There have been reports of serotonin syndrome when SSRIs have been given with lithium or tryptophan, therefore, the concomitant use of fluoxetine with these drugs should be undertaken with caution. When fluoxetine is used in combination with lithium, closer and more frequent clinical monitoring is required.

Protein binding

Because fluoxetine is tightly bound to plasma protein, the administration of fluoxetine to a patient taking another medicine that is tightly bound to protein may cause a shift in plasma concentrations of either medicine.

Drugs that interfere with haemostasis

Caution is advised in patients with a history of bleeding disorders as well as in patients taking SSRIs, particularly in concomitant use with oral anticoagulants, medicines known to affect platelet function (e.g. atypical antipsychotics such as clozapine, phenothiazines, most TCAs, aspirin, NSAIDs) or other drugs that may increase risk of bleeding.

Warfarin

Altered anti-coagulant effects (laboratory values and/or clinical signs and symptoms), with no consistent pattern, but including increased bleeding, have been reported uncommonly when fluoxetine is co-administered with warfarin. As is prudent in concomitant use of warfarin with many other medicines, patients receiving warfarin therapy should receive careful coagulation monitoring when fluoxetine is initiated or stopped.

Electroconvulsive therapy (ECT)

There have been rare reports of prolonged seizures in patients on fluoxetine receiving ECT treatment.

Elimination half-life

The long elimination half-lives of fluoxetine and its principal metabolite, norfluoxetine, are of potential consequence when medicines are prescribed which might interact with either substance following the discontinuation of fluoxetine.

Tamoxifen

Pharmacokinetic interaction between CYPIID6 inhibitors and tamoxifen showing a 65-75% reduction in plasma levels of one of the more active forms of tamoxifen (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 CYPIID6 inhibitors (including fluoxetine) should be avoided when possible.

Alcohol

The combination of SSRI treatment and alcohol is not advisable. As with other psychotropic drugs, patients should be advised to avoid alcohol use while taking fluoxetine.

St John’s Wort

An increase in serotonergic effects, such as serotonin syndrome may occur when selective serotonin reuptake inhibitors and herbal preparations containing St John’s Wort (*Hypericum perforatum*) are used together.

4.6 Fertility, pregnancy and lactation

Pregnancy

Fluoxetine use should be considered during pregnancy only if the potential benefit justifies the potential risk to the foetus, taking into account the risks of untreated depression.

Experimental animal studies do not indicate direct or indirect harmful effects, with respect to the development of the embryo or foetus or the course of gestation. Because animal reproduction studies are not always predictive of human response, this medicine should be used during pregnancy only if clearly needed. This drug crosses the placenta.

Results of a number of epidemiological studies assessing the risk of fluoxetine exposure in early pregnancy have been inconsistent and have not provided conclusive evidence of an increased risk of congenital malformations. However, one meta-analysis suggests a potential risk of cardiovascular defects in infants of women exposed to fluoxetine during the first trimester of pregnancy compared to infants of women who were not exposed to fluoxetine.

At the end of pregnancy, caution should be exercised, as transitory withdrawal symptoms (e.g. transient jitteriness, difficulty feeding, tachypnea and irritability) have been reported rarely in the neonate after maternal use near term.

Neonates exposed to fluoxetine and other SSRIs or serotonin and noradrenaline reuptake inhibitors (SNRIs), late in the third trimester have been uncommonly reported to have clinical findings of respiratory distress, cyanosis, apnoea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycaemia, hypotonia, hypertonia, hyperreflexia, tremor, jitteriness, irritability and constant crying. Such events can arise immediately upon delivery and are usually transient. These features could be consistent with either a direct effect of SSRIs and SNRIs or, possibly, a drug discontinuation syndrome. When treating a pregnant woman with fluoxetine during the third trimester, the physician should carefully consider the potential risks and benefits of treatment.

Although untreated depression is a risk factor for preterm delivery, epidemiological data suggests that the use of SSRIs and SNRIs in pregnancy may be associated with a further additional increased risk of pre-term delivery.

Although there is no consistent evidence epidemiological data have suggested that the use of SSRIs in pregnancy, particularly in late pregnancy, may increase the risk of persistent pulmonary hypertension in the newborn (PPHN). In the general population PPHN occurs in 1 to 2 per 1000 live births and the increase in absolute risk with treatment would be very small. This potential risk should be weighed against the need for treatment during pregnancy.

Labour and delivery

Observational data suggests an increased risk (less than 2-fold) of postpartum haemorrhage following fluoxetine exposure (near delivery). Epidemiological data suggests that the use of SSRIs and SNRIs in pregnancy may be associated with a small but statistically significant increase in pre-term delivery.

Breast-feeding

Fluoxetine is excreted in human milk; therefore, caution should be exercised when fluoxetine is administered to nursing women.

Fertility

Impairment of fertility in adult animals at doses up to 12.5 mg/kg/day (approximately 1.5 times the MRHD on a mg/m^2 basis) was not observed (see section 5.3).

4.7 Effects on ability to drive and use machines

Psychoactive medicines may impair judgement, thinking, or motor skills. Patients should be advised to avoid driving a car or operating machinery until they are reasonably certain that their performance is not affected.

4.8 Undesirable effects

Summary of the safety profile

Adverse reactions are dose-dependent and more common at higher doses than 20 mg per day.

Associated with discontinuation of treatment

Fifteen percent of approximately 4,000 patients who received fluoxetine hydrochloride in U.S. premarketing clinical trials discontinued treatment due to an adverse event. The more common events causing discontinuation included: psychiatric (5.3%), primarily nervousness, anxiety and insomnia; digestive (3.0%), primarily nausea; nervous system (1.6%), primarily dizziness; body as a whole (1.5%), primarily asthenia and headache; and skin (1.4%), primarily rash and pruritus.

In obsessive compulsive disorder studies, 12.1% of fluoxetine treated patients discontinued treatment early because of adverse events. Anxiety and rash at incidences of less than 2% were the most frequently reported events.

Adverse reactions from clinical trials

Very common adverse events are defined as those occurring in 1 or more occasions in at least 1/10 patients; common adverse events are defined as those occurring in 1 or more occasions in at least 1/100 patients; uncommon adverse events are those occurring in 1/100 to 1/1000 patients; rare events are those occurring in less than 1/1000 patients; very rare events are those occurring in less than 1/10000 patients. It is important to emphasise that, although the events reported did occur during treatment with fluoxetine, they were not necessarily caused by it.

Cardiac disorders

Common:	palpitations, vasodilatation
Uncommon:	hypotension
Very Rare:	orthostatic hypotension

Vascular disorders

Rare:	vasculitis

Gastrointestinal disorders

Very Common:	diarrhoea, nausea
Common:	anorexia, dyspepsia, gastrointestinal disorder (includes oesophageal varices haemorrhage, gingival and mouth bleeding, haematemesis, haematochezia, haematomas [intraabdominal, peritoneal], haemorrhage [anal, oesophageal, gastric, gastrointestinal (upper and lower), haemorrhoidal, peritoneal, rectal], haemorrhagic diarrhoea and enterocolitis, haemorrhagic diverticulitis, haemorrhagic gastritis, melaena, and ulcer haemorrhage [oesophageal, gastric, duodenal]), mouth dryness, vomiting, taste perversion
Uncommon:	dysphagia
Rare:	oesophageal pain

Blood and lymphatic system disorders

Uncommon:	ecchymosis
Rare:	serum sickness, anaphylactoid reaction

Metabolic and nutritional disorders

Common:	weight loss

Musculoskeletal disorders

Uncommon:	twitching

Nervous system disorders

Very Common:	anxiety, dizziness, headache, insomnia, nervousness, somnolence, tremor; fatigue (includes asthenia)
Common:	abnormal dreams, libido decreased, sleep disorder, thinking abnormal, chills
Uncommon:	feeling abnormal, akathisia (see section 4.4), ataxia, balance disorder, bruxism, buccoglossal syndrome, depersonalisation, dyskinesia, manic reaction, myoclonus, seizures, psychomotor hyperactivity
Very Rare:	mild intensity headache, serotonin syndrome (see section 4.4, neuroleptic malignant syndrome-like effects)

Respiratory disorders

Common:	yawn

Skin and subcutaneous tissue disorders

Common:	allergic reaction, pruritus, rash, sweating, urticaria
Uncommon:	alopecia
Rare:	photosensitivity reaction

Eye disorders

Common:	abnormal vision
Uncommon:	mydriasis

Renal and urinary disorders

Common:	urinary frequency
Uncommon:	urination impaired

Reproductive system and breast disorders

Common:	abnormal ejaculation (male only), gynaecological bleeding (female only), impotence (male only)
Uncommon:	anorgasmia, breast pain, sexual dysfunction (occasionally persisting after treatment discontinuation)
Rare:	priapism (male only)

Investigations

Common:	Electrocardiogram data: QT interval prolongation (QTcF ≥ 450 msec)

Children and adolescents:

Common:	epistaxis

(Very rare) Weight loss and decreased height gain: As with other SSRIs, decreased weight gain has been observed in association with the use of fluoxetine in children and adolescent patients. After 19 weeks of treatment in a clinical trial, paediatric subjects treated with fluoxetine gained an average of 1.1 cm less in height ($p = 0.004$) and 1.1 kg less in weight ($p = 0.008$) than subjects treated with placebo. Fluoxetine treatment was also associated with a decrease in serum alkaline phosphatase levels in this study.

In a retrospective matched control observational study with a mean of 1.8 years of exposure to fluoxetine, paediatric subjects treated with fluoxetine had no difference in growth (0.0 cm) adjusted for expected growth in height from their matched, untreated controls (95% CI: -0.6 to 0.6, $p = 0.9673$). Limited evidence is available concerning the longer-term effects of fluoxetine on the development and maturation of children and adolescent patients. Height and weight should be monitored periodically in paediatric patients receiving fluoxetine.

Adverse reactions from spontaneous reporting

The following events have not been reported in clinical trials of fluoxetine but have been reported in clinical practice and are possibly related to fluoxetine therapy. All these events are classified as very rare (occurring in less than 1/10000 patients) (except haemorrhagic manifestations which is classified as rare (occurring in less than 1/1000 patients)).

Body as a whole

Very rare: malignant hyperthermia, Stevens-Johnson syndrome, erythema multiforme

Cardiac disorders

Very rare: angioedema

Gastrointestinal disorders

Very rare: gastrointestinal bleeding

Hepatobiliary disorders

Very rare: abnormal hepatic function, aggravation of hepatic damage, hepatic failure/necrosis, idiosyncratic hepatitis

Endocrine disorders

Very rare: inappropriate secretion of antidiuretic hormone

Blood and lymphatic system disorders

Rare: haemorrhagic manifestations (e.g. gynaecological haemorrhages, gastrointestinal bleedings and other cutaneous or mucous bleedings) (see section 4.4)

Very rare: eosinophilia, thrombocytopenic purpure

Psychiatric and nervous system disorders

Very rare: oculogyric crisis, tardive dyskinesia, memory impairment

Discontinuation symptoms have been reported when fluoxetine treatment is stopped. The most commonly reported symptoms include dizziness, sleep disorders, sensory disturbances/paraesthesia, anxiety, agitation, asthenia, confusion, headache, and irritability.

Skin and subcutaneous tissue disorders

Very rare: epidermal necrolysis

Reproduction system and breast disorders

Very rare: enlarged clitoris, gynaecomastia, galactorrhoea, hyperprolactinaemia

Post-marketing experiences

The following events have occurred with post-marketing use of fluoxetine, frequencies unknown:

Decreased appetite, hyponatraemia, hallucinations, agitation, panic attacks, suicidal thoughts and behaviour, confusion, disturbance in attention, lethargy, tinnitus, dyspnoea, pharyngitis, aggression, extrapyramidal syndrome and weight gain.

Class Effects

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 this risk is unknown.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://pophealth.my.site.com/carmreportnz/s/.

4.9 Overdose

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 Torsade 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.

Cardiac and vital signs monitoring is 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. In managing overdosage, consider the possibility of multiple medicine involvement.

For risk assessment and advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764 766).

5. Pharmacological Properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Selective serotonin reuptake inhibitors

ATC code: N06AB03

FLUOX is an antidepressant intended for oral administration.

Mechanism of action

Fluoxetine is a selective inhibitor of serotonin reuptake, its presumed mechanism of action. Fluoxetine has practically no affinity to other receptors such as α_1-, α_2- and β-adrenergic; serotonergic; dopaminergic; histaminergic; muscarinic; and GABA receptors.

Pharmacodynamic effects

The aetiology of premenstrual dysphoric disorder is unknown, but endogenous steroids (neuro and/or ovarian) involved in the menstrual cycle may interrelate with neuronal serotonergic activity.

Clinical efficacy and safety

Clinical data premenstrual dysphoric disorder (PMDD): In clinical trials fluoxetine was shown to be effective in relieving both the cyclical mood changes and physical symptoms (tension, irritability and dysphoria, bloating and breast tenderness) associated with PMDD.

5.2 Pharmacokinetic properties

Absorption

Fluoxetine is well absorbed after oral administration. Peak plasma concentration is reached in six to eight hours. Steady-state plasma concentrations are achieved after dosing for several weeks. Steady-state concentrations after prolonged dosing are similar to concentrations seen at four to five weeks.

Distribution

Fluoxetine is extensively bound to plasma proteins. Fluoxetine is widely distributed.

Biotransformation

Fluoxetine is extensively metabolized in the liver to norfluoxetine and a number of other, unidentified metabolites which are excreted in urine.

Elimination

The elimination half-life of fluoxetine is four to six days and that of its active metabolite is four to 16 days.

5.3 Preclinical safety data

Carcinogenicity and mutagenicity

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

Impairment of fertility

In a juvenile toxicology study in CD rats, administration of 30 mg/kg of fluoxetine hydrochloride on postnatal days 21 through 90 resulted in increased serum activities of creatine kinase (CK) and aspartate aminotransferase (AST), which were accompanied microscopically by skeletal muscle degeneration, necrosis and regeneration. Other findings in rats administered 30 mg/kg included degeneration and necrosis of seminiferous tubules of the testis, epididymal epithelial vacuolation, and immaturity and inactivity of the female reproductive tract. Plasma levels achieved in these animals at 30 mg/kg were approximately 5 to 8 fold (fluoxetine) and 18 to 20 fold (norfluoxetine), and at 10 mg/kg approximately 2 fold (fluoxetine) and 8 fold (norfluoxetine) higher compared to plasma concentrations usually achieved in paediatric patients. Following an approximate 11-week recovery period, sperm assessments in the 30 mg/kg males only, indicated an approximately 30% decrease in sperm concentrations without affecting sperm morphology or motility. Microscopic evaluation of testes and epididymides of these 30 mg/kg males indicated that testicular degeneration was irreversible. Delays in sexual maturation occurred in the 10 mg/kg males and in the 30 mg/kg males and females. The significance of these findings in humans is unknown. Femur length at 30 mg/kg increased to a lesser extent compared with control rats.

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.

Human case reports with some SSRIs have shown that an effect on sperm quality is reversible. Impact on human fertility has not been observed so far.

6. Pharmaceutical Particulars

6.1 List of excipients

FLUOX capsules also contain:

Capsule fill:

- Lactose monohydrate
- maize starch
- colloidal anhydrous silica
- purified talc
- magnesium stearate

Capsule shell:

- shellac
- ethanol
- isopropyl alcohol
- n-butyl alcohol

- propylene glycol
- ammonium hydroxide
- potassium hydroxide
- iron oxide black
- brilliant blue FCF
- quinoline yellow FCF
- titanium dioxide
- indigo carmine
- erythrosine
- gelatin
- sodium lauryl sulfate

FLUOX dispersible tablets also contain:

- microcrystalline cellulose
- crospovidone
- maize starch
- saccharin sodium
- colloidal anhydrous silica
- magnesium stearate
- menthol
- peppermint oil
- arabic gum
- maltodextrin

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

FLUOX capsules: 2 years

FLUOX dispersible tablets: 2 years

6.4 Special precautions for storage

Store at or below 25°C.

6.5 Nature and contents of container

FLUOX capsules: PVC/PVDC/Al blister packs. Pack-sizes of 30, 84 or 90 capsules.

FLUOX dispersible tablets: PVC/PE/PVDC/Al blister packs. Pack-sizes of 28 or 30 dispersible tablets.

Not all dosage forms or pack sizes may be marketed.

6.6 Special precautions for disposal

Not applicable.

7. Medicines Schedule

Prescription Medicine

8. Sponsor Details

Viatris Ltd
PO Box 11-183
Ellerslie
AUCKLAND
www.viatris.co.nz
Telephone: 0800 168 169

9. Date of First Approval

FLUOX capsules: 18 November 1999

FLUOX dispersible tablets: 18 July 2002

10. Date of Revision of the Text

24 April 2026

Summary table of changes

Section	Summary of new information
2	Excipients with known effect information updated to align with new Medsafe requirements.
6.3	Shelf-life increase for the Fluox dispersible tablets
6.5	Minor editorial change
10	Updated date of revision