NEW ZEALAND DATA SHEET

1. PROZAC®

PROZAC 20 mg capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains fluoxetine hydrochloride equivalent to 20 mg fluoxetine.

For the full list of excipients, see Section 6.1 List of excipients

3. PHARMACEUTICAL FORM

PROZAC 20 capsules are presented as size 3, green/cream capsules bearing the identicode "Lilly 3105" printed in black ink on both the capsule cap and base.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Depression and its associated anxiety,

Bulimia nervosa,

Obsessive-Compulsive disorder and

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

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.

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

Age

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

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

Paediatric population

While clinical studies have been conducted in children and adolescents, the use of PROZAC 20 is not recommended in this population. (See Section 4.4 Special warnings and precautions for use, Clinical Worsening and Suicide Risk, 5.3 Impairment of Fertility and 4.8 Undesirable effects).

Method of administration

PROZAC 20 may be administered with or without food.

4.3 Contraindications

PROZAC 20 is contraindicated in patients known to be hypersensitive to fluoxetine or any of the excipients listed in Section 6.1 List of excipients.

PROZAC 20 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 PROZAC 20 and initiation of therapy with a MAOI. If PROZAC 20 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 PROZAC 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 nonpsychiatric. 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 PROZAC 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 Interactions with other medicines and other forms of interactions). Another factor associated with QTc prolongation is a family history of QTc prolongation.

In high risk patients (eg 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 >500ms or increases by >60ms.

Rash

Rash, anaphylactoid events, and progressive systemic events, sometimes serious and involving skin, kidney, liver or lung have been reported in patients taking PROZAC 20. Upon the appearance of rash, or of other possible allergic phenomena for which an alternative aetiology cannot be identified PROZAC 20 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, PROZAC 20 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 PROZAC 20 and hyperglycaemia has developed following discontinuation. Insulin and/or oral hypoglycaemic dosage may need to be adjusted when PROZAC 20 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 Undesirable effects) and postpartum haemorrhage (see Section 4.6 Fertility, pregnancy and lactation). 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 SSRI's. 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 SSRI's, particularly in concomitant use with oral anticoagulants, drugs known to affect platelet function (e.g. atypical antipsychotics such as clozapine, phenothiazines, most TCA's, aspirin, NSAID's) or other drugs that may increase risk of bleeding.

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

Serotonin syndrome

Development of serotonin syndrome may occur in association with treatment with SSRIs, particularly when given in combination with MAOIs (see section 4.3) or other serotonergic agents such as tramadol.

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 PROZAC should be discontinued if such events occur and supportive symptomatic treatment initiated.

Information for Patients and Families

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

Because PROZAC 20 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 Interactions with other medicines and other forms of interactions

Monoamine Oxidase Inhibitors

See Section 4.3 Contraindications.

Medicines Metabolised 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 PROZAC 20 concurrently or has taken it in the previous five weeks. If PROZAC 20 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 tramadol) may result in serotonin syndrome (see section 4.4).

Protein binding

Because fluoxetine is tightly bound to plasma protein, the administration of PROZAC 20 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 SSRI's, particularly in concomitant use with oral anticoagulants, medicines known to affect platelet function (e.g. atypical antipsychotics such as clozapine, phenothiazines, most TCA's, aspirin, NSAID's) 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 PROZAC 20 is co-administered with warfarin. As is prudent in concomitant use of warfarin with many other drugs, patients receiving warfarin therapy should receive careful coagulation monitoring when PROZAC 20 is initiated or stopped.

Electroconvulsive therapy (ECT)

There have been rare reports of prolonged seizures in patients on PROZAC 20 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 PROZAC 20.

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 PROZAC 20.

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).

Breast-feeding

Fluoxetine is excreted in human milk; therefore, caution should be exercised when PROZAC 20 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/m2 basis) was not observed.

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

a. 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.

b. 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.

Blood and lymphatic system disorders - Uncommon: ecchymosis; Rare: serum sickness, anaphylactoid reaction

Metabolic and nutritional disorders - Common: weight loss.

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, ataxia, balance disorder, bruxism, buccoglossal syndrome, depersonalisation, dyskinesia, manic reaction, myoclonus, seizures, psychomotor hyperactivity; Very Rare: mild intensity headache, serotonin syndrome (neuroleptic malignant syndrome-like effects),

Eye disorders – Common: abnormal vision; Uncommon: mydriasis.

Cardiac disorders - Common: palpitations, vasodilatation; Uncommon: Hypotension; Very Rare: orthostatic hypotension.

Vascular disorders: Rare: vasculitis

Respiratory disorders - Common: yawn.

Gastrointestinal disorders - Very Common: diarrhoea, nausea; Common: anorexia, dyspepsia, gastrointestinal disorder (includes oesophageal varices haemorrhage, gingival and mouth bleeding, hematemesis, hematochezia, hematomas [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.

Skin and subcutaneous tissue disorders - Common: allergic reaction, pruritus, rash, sweating, urticaria; Uncommon: alopecia; Rare: photosensitivity reaction.

Musculoskeletal disorders - Uncommon: twitching.

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 (0.0cm) 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.

c. 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)).

Blood and lymphatic system disorders - eosinophilia, thrombocytopenic purpure; Rare: haemorrhagic manifestations (e.g. gynaecological haemorrhages, gastrointestinal bleedings and other cutaneous or mucous bleedings) (see Section 4.4 Special warnings and precautions for use, Haemorrhage).

Endocrine disorders - inappropriate secretion of antidiuretic hormone.

Psychiatric and nervous system disorders - 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.

Cardiac disorders - angioedema

Gastrointestinal disorders – gastrointestinal bleeding

Hepatobiliary disorders – abnormal hepatic function, aggravation of hepatic damage, hepatic failure/necrosis, idiosyncratic hepatitis

Skin and subcutaneous tissue disorders - epidermal necrolysis.

Reproduction System and Breast Disorders - enlarged clitoris, gynaecomastia, galactorrhea, hyperprolactinemia

Body as a Whole - malignant hyperthermia, Stevens-Johnson syndrome, erythema multiforme.

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://nzphvc.otago.ac.nz/reporting/

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 advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

PROZAC 20 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 α1-, α2- and ß-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 metabolised 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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Dimeticone

Ink

Iron oxide yellow

Patent blue V

Titanium dioxide

Starch

Gelatin

6.2 Incompatibilities

Not applicable

6.3 Shelf-life

Three years

6.4 Special precautions for storage

Store below 30°C

6.5 Nature and contents of container

Each blister pack contains 28 capsules.

6.6 Special precautions for disposal and other handling

Any unused medicine or waste material should be disposed of in accordance with local requirements.

7. MEDICINE SCHEDULE

Prescription Medicine

8. SPONSOR

Eli Lilly and Company (NZ) Limited
PO Box 109 197
Newmarket, Auckland 1149
New Zealand

Contact telephone number: 0800 500 056

9. DATE OF FIRST APPROVAL

4 February 1988

10. DATE OF REVISION OF THE TEXT

28 September 2022

11. SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
All	Minor Editorial changes throughout the Data sheet
4.4	Addition of information on Serotonin syndrome
4.5	Addition of the sub heading “Serotonergic drugs”, and revision of text to align with section 4.4

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