AUSTRALIAN PRODUCT INFORMATION

ZACTIN®

(fluoxetine hydrochloride) capsule

VIATRIS

1 NAME OF THE MEDICINE

Fluoxetine hydrochloride

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ZACTIN capsule contains fluoxetine hydrochloride equivalent to fluoxetine 20 mg (64.7 micromol).

Excipients with known effect: sulfites and sugars as lactose.

For the full list of excipients, see Section 6.1 LIST OF EXCIPIENTS.

3 PHARMACEUTICAL FORM

ZACTIN fluoxetine 20mg (as hydrochloride) capsules are size 3 capsule with light green opaque body and purple opaque cap, printed "FL20" on the body and the "α" symbol on the cap in black ink.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Treatment of:

- Major depression.
- Obsessive Compulsive Disorder (OCD).

4.2 DOSE AND METHOD OF ADMINISTRATION

Dosage

Depression

The usual recommended initial dose of fluoxetine in the treatment of depression is 20 mg/day, taken in the morning.

A dose increase may be considered after several weeks if no clinical improvement is observed. Doses above 20 mg/day should be administered twice daily (morning and noon) and should not exceed a maximum daily dose of 80 mg (see Section 5.2 PHARMACOKINETIC PROPERTIES - Clinical issues related to accumulation and slow elimination).

As with other antidepressant agents, the full antidepressant effect may be delayed until 4 or more weeks of therapy (see Section 5.2 PHARMACOKINETIC PROPERTIES - Clinical issues related to accumulation and slow elimination).

As with many other medications, patients with renal and/or hepatic impairment should be given a lower or less frequent dosage (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION- Dosage adjustment). A lower or less frequent dosage should also be considered for patients, such as the elderly, with concurrent disease or on multiple medications (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE - Use in the elderly, Use in patients with concomitant illness).

Obsessive compulsive disorder (OCD)

Initial treatment - A dose of 20 mg/day, administered in the morning, is recommended as the initial dose. If insufficient clinical improvement is observed, a dose increase may be considered after several weeks. The full therapeutic effect may be delayed until 5 weeks of treatment or longer.

Doses above 20 mg/day may be administered on a once a day (i.e., morning) or b.i.d. schedule (i.e., morning and noon). A dose range of 20 to 60 mg/day is recommended, however, doses of up to 80 mg/day have been well tolerated in open studies of OCD. The maximum fluoxetine dose should not exceed 80 mg/day.

A lower or less frequent dosage should be used in patients with renal and/or hepatic impairment (see Section see Section 4.2- DOSE AND METHOD OF ADMINISTRATION - Dosage adjustment). A lower or less frequent dosage should also be considered for patients, such as the elderly, with concurrent disease or on multiple medications (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE - Use in the elderly, Use in patients with concomitant illness).

Maintenance/continuation treatment - While there are no systematic studies that answer the question of how long to continue fluoxetine, OCD is a chronic condition and it is reasonable to consider continuation for a responding patient.

However, dosage adjustments should be made to maintain the patient on the lowest effective dosage and patients should be periodically reassessed to determine the need for treatment.

Method of administration

For oral administration. The capsule should be swallowed whole with a glass of water.

Dosage adjustment

Hepatic impairment

As might be predicted from its primary site of metabolism, liver impairment can affect the elimination of fluoxetine. The elimination half-life of fluoxetine was prolonged in a study of cirrhotic patients, with a mean of 7.6 days compared to the range of 2 to 3 days seen in subjects without liver disease; norfluoxetine elimination was also delayed, with a mean duration of 12 days for cirrhotic patients compared to the range of 7 to 9 days in normal subjects. This suggests that the use of fluoxetine in patients with liver disease must be approached with caution. If fluoxetine is administered to patients with liver disease, a lower or less frequent dose should be used.

Renal impairment

In depressed patients on dialysis (N=12), fluoxetine administered as 20 mg once daily for two months produced steady-state fluoxetine and norfluoxetine plasma concentrations comparable to those seen in patients with normal renal function. While the possibility exists that renally excreted metabolites of fluoxetine may accumulate to higher levels in patients with severe renal dysfunction, use of a lower or less frequent dose is not routinely necessary in renally impaired patients.

Age

Adjustment of dosage should not be required on the basis of age alone (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE - Hepatic impairment, Renal impairment, Use in Patients with Concomitant Illness and Section 4.5 INTERACTION WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

Children and adolescents (<18 years)

The safety and efficacy of fluoxetine for the treatment of children and adolescents less than 18 years of age has not been established.

4.3 CONTRAINDICATIONS

ZACTIN is contraindicated in patients known to be hypersensitive to fluoxetine hydrochloride or any of the other ingredients in the formulation.

Monoamine oxidise inhibitors

The combined administration of fluoxetine and a monoamine oxidase inhibitor (MAOI) has been associated with the development of serotonin syndrome, a serious, sometimes fatal, reaction in patients receiving an SSRI in combination with a MAOI and in patients treated with fluoxetine and a MAOI in close temporal proximity. Some cases presented with features resembling neuroleptic malignant syndrome. Symptoms and signs of serotonin syndrome include: clonus, myoclonus, tremor, shivering, hyperreflexia, hyperthermia, rigidity, autonomic instability with possible rapid fluctuations of vital signs and mental status changes that include extreme agitation progressing to delirium and coma.

Therefore, fluoxetine should not be used in combination with a MAOIs (selective, reversible or irreversible), or within a minimum of 14 days of discontinuing therapy with a MAOI. Since fluoxetine and its major metabolite have very long elimination half-lives, at least 5 weeks (perhaps longer, especially if fluoxetine has been prescribed chronically and/or at higher doses - see Section 5.2 PHARMACOKINETIC PROPERTIES - Accumulation and slow elimination) should be allowed after stopping fluoxetine hydrochloride before starting a MAOI. Limited reports suggest that orally administered cyproheptadine (Periactin®) or intravenously administered dantrolene (Dantrium®) may benefit patients experiencing such reactions. Animal studies also suggest that cyproheptadine may be beneficial.

Pimozide

Concomitant use in patients taking pimozide is contraindicated (see Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS - CNS active drugs).

Metoprolol

Fluoxetine is contraindicated in combination with metoprolol used in cardiac failure (see Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS - Metoprolol used in cardiac failure).

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Sexual dysfunction

Selective serotonin reuptake inhibitors (SSRIs)/serotonin norepinephrine reuptake inhibitors (SNRIs) may cause symptoms of sexual dysfunction (see section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS) - Events observed during therapy with fluoxetine - clinical trials). There have been reports of long-lasting sexual dysfunction where the symptoms have continued despite discontinuation of SSRIs/SNRI.

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

Serotonin syndrome

Development of serotonin syndrome may occur in association with treatment with SSRIs and SNRIs, particularly when given in combination with MAOIs or other serotonergic agents. Symptoms and signs 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 hydrochloride should be discontinued if such events occur and supportive symptomatic treatment initiated.

Cardiovascular effects

QT prolongation can occur with fluoxetine treatment. Fluoxetine should be used with caution in patients with conditions such as congenital long QT syndrome; acquired long QT syndrome (e.g. due to concomitant use of a drug that prolongs the QT); a family history of QT prolongation; or other clinical conditions that predispose to arrhythmias (e.g. hypokalaemia or hypomagnesemia) or increased exposure to fluoxetine (e.g. hepatic impairment).

Rash and possibly allergic events

During premarketing testing of more than 5,600 US patients treated with fluoxetine, approximately 4% developed a rash and/or urticaria. Almost a third of these cases were withdrawn from treatment because of the rash and/or systemic signs or symptoms associated with the rash. Clinical findings reported in association with

rash include fever, arthralgias, leucocytosis, carpal tunnel syndrome, oedema, respiratory distress, proteinuria, lymphadenopathy, and mild transaminase elevation. Most patients improved promptly with discontinuation of fluoxetine and/or adjunctive treatment with antihistamines or steroids, and all patients experiencing these events were reported to recover completely.

Two patients are reported to have developed a serious cutaneous systemic illness. One was considered to have a leucocytoclastic vasculitis, and the other, a severe desquamating syndrome which was considered variously to be a vasculitis or erythema multiforme, although in neither patient was there an unequivocal diagnosis. Several other patients have had systemic syndromes suggestive of serum sickness.

Since the introduction of fluoxetine, systemic events possibly related to vasculitis have developed in patients with rash. Although these events are rare, they may be serious, involving the lung, kidney, or liver. Death has been reported to occur in association with these systemic events.

Anaphylactoid events, including urticaria, bronchospasm, and angioedema, alone and in combination, have been reported.

Pulmonary events, including inflammatory processes of varying histopathology and/or fibrosis, have been rarely reported. These events have occurred with dyspnoea as the only preceding symptom.

It is not known whether these systemic events and rash have a common underlying cause or are due to different aetiologies or pathogenic processes. Fluoxetine should be discontinued upon the appearance of rash or of other possibly allergic phenomena for which an alternative cause cannot be identified.

Anxiety and insomnia

10 to 15% of patients receiving fluoxetine reported anxiety, nervousness and insomnia. These symptoms led to drug discontinuation in 5% of patients treated with fluoxetine.

Altered appetite and weight

Significant weight loss, especially in underweight depressed patients, may be an undesirable result of treatment with fluoxetine.

In controlled clinical trials, approximately 9% of patients treated with fluoxetine experienced anorexia. This incidence is approximately six times that seen in placebo controls. A weight loss of greater than 5% of bodyweight occurred in 13% of fluoxetine treated patients compared to 4% of placebo and 3% of tricyclic antidepressant treated patients. However, fluoxetine has only rarely been discontinued due to weight loss.

Screening for bipolar disorder

A major depressive episode may be the initial presentation of bipolar disorder. It is generally believed that treating such an episode with an antidepressant alone may increase the likelihood of precipitation of a mixed/manic episode in patients at risk of bipolar disorder. Prior to initiating treatment with an antidepressant, patients should be adequately screened to determine if they are at risk for bipolar disorder; such screening should include a detailed psychiatric history, including a family history of suicide, bipolar disorder, and depression.

Activation of mania/hypomania

Hypomania or mania occurred in about 1% of patients who received fluoxetine during premarketing testing. Activation of mania/hypomania has also been reported in a small percentage of patients with major affective disorder treated with other marketed antidepressants.

Seizures

Among more than 6,000 patients evaluated worldwide during premarketing development of fluoxetine, 12 patients experienced convulsions (or events described as possibly having been seizures).

Convulsions/seizures associated with other marketed antidepressants appear to occur at a similar rate (0.2%). Therefore, fluoxetine should be introduced with care in patients with a history of seizures.

The long elimination half-lives of fluoxetine and its metabolites

Because of the long elimination half-lives of fluoxetine (1 to 3 days after acute dosing and 4 to 6 days after chronic dosing) and its major active metabolite, norfluoxetine (4 to 16 days on both acute and chronic dosing), dose changes will not be fully reflected in plasma concentrations for several weeks, affecting both strategies for titration to final dose and withdrawal from treatment (see Section 5.2 PHARMACOKINETIC PROPERTIES and Section 4.2 DOSAGE AND METHOD OF ADMINISTRATION).

Withdrawal reactions

Withdrawal reactions have been reported with selective serotonin reuptake inhibitors (SSRIs). Due to 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.

Tamoxifen

Some studies have shown that the efficacy of tamoxifen, as measured by the risk of breast cancer relapse, may be reduced when co-prescribed with fluoxetine as a result of inhibition of CYP2D6 (see Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS). This risk may increase with longer duration of co-administration. When tamoxifen is used for the treatment or prevention of breast cancer, prescribers should consider using an alternative anti-depressant with little or no CYP2D6 inhibition.

Use in patients with concomitant illness

Clinical trial experience with fluoxetine in patients with concomitant systemic illness is limited. In patients with diseases or conditions which could affect metabolism or haemodynamic responses, fluoxetine should be used with caution.

Fluoxetine has not been evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or unstable heart disease. Patients with these diagnoses were systematically excluded from clinical studies during the product's premarket testing. However, the electrocardiograms of 312 patients who received fluoxetine in double blind trials were retrospectively evaluated and no conduction abnormalities resulting in heart block were observed. The mean heart rate was decreased by approximately 3 beats/minute.

In subjects with liver cirrhosis, the clearances of fluoxetine and norfluoxetine, were reduced, thus increasing the elimination half-lives of these substances. A lower or less frequent dose should be used in these patients.

Since fluoxetine is extensively metabolised, excretion of unchanged drug in urine is a minor route of elimination. However, until adequate numbers of patients with severe renal impairment have been evaluated during chronic treatment with fluoxetine, it should be used with caution in such patients.

Fluoxetine may alter the glycaemic control of patients with diabetes. Hypoglycaemia has occurred during therapy with fluoxetine and hyperglycaemia has developed following cessation of the drug. Thus, in diabetic patients, the dosage of insulin and/or oral hypoglycaemics may need to be adjusted when therapy with fluoxetine is commenced 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 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)) and postpartum haemorrhage (see Section 4.6 FERTILITY, PREGNANCY AND LACTATION). Other haemorrhagic manifestations (e.g. gynaecological haemorrhages and other cutaneous or mucous bleedings) have been reported rarely. 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.

Information for patients

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

- Because fluoxetine hydrochloride may impair judgment, 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 drugs or alcohol.
- Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during therapy.
- Patients should be advised to notify their physician if they are breastfeeding.
- Patients should be advised to notify their physician if they develop a rash or hives.

Hyponatraemia

Several cases of hyponatraemia (some with serum sodium lower than 110 mmol/L) have been reported. The hyponatraemia appeared to be reversible when fluoxetine was discontinued. Although these cases were complex with varying possible aetiologies, some were possibly due to the syndrome of inappropriate antidiuretic hormone secretion (SIADH). Most of these occurrences have been in older patients and in patients taking diuretics or who were otherwise volume depleted. Ten of 313 fluoxetine patients and 6 of 320 placebo recipients in a placebo controlled, double blind trial, had a reduction in serum sodium below the reference range. This difference was not statistically significant. The lowest observed concentration was 129 mmol/L. The observed decreases were not clinically significant in this trial.

Hyponatraemia in the elderly. There have been seven reports (total 5,628) of hyponatraemia (serum sodium 114 to 128 mmol/L) in elderly patients receiving fluoxetine 20 mg daily. In five patients hyponatraemia occurred within 19 days of starting fluoxetine, however in all cases, the patients recovered after fluoxetine was withdrawn. Hence, in elderly patients, it may be advisable to monitor electrolyte levels during the initial weeks of therapy.

Platelet function

There have been reports of altered platelet function and/or abnormal results from laboratory studies in patients taking fluoxetine. While there have been reports of abnormal bleeding in several patients taking fluoxetine, it is unclear whether fluoxetine had a causative role.

Electroconvulsive therapy (ECT)

There are no clinical studies establishing the benefit of the combined use of ECT and fluoxetine. There have been some reports of prolonged seizures in patients on fluoxetine receiving ECT treatment.

Drug abuse and dependence

Physical and psychological dependence - fluoxetine hydrochloride has not been systematically studied, in animals or humans, for its potential for abuse, tolerance or physical dependence. While the premarketing clinical experience with fluoxetine hydrochloride did not reveal any tendency for a withdrawal syndrome or any drug seeking behaviour, these observations were not systematic and it is not possible to predict on the basis of this limited experience the extent to which a CNS active drug will be misused, diverted and/or abused once marketed. Consequently, physicians should carefully evaluate patients for a history of drug abuse and follow such patients closely, observing them for signs of fluoxetine misuse or abuse (e.g. development of tolerance, incrementation of dose, drug-seeking behaviour).

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.

Use in hepatic impairment

See Section 4.2 DOSE AND METHOD OF ADMINISTRATION.

Use in renal impairment

See Section 4.2 DOSE AND METHOD OF ADMINISTRATION.

Use in the elderly

Evaluation of patients over the age of 60 who received fluoxetine 20 mg daily revealed no unusual pattern of adverse events relative to the clinical experience in younger patients. These data are insufficient, however, to dismiss the possibility of age-related differences during chronic use, particularly in elderly patients who have concomitant systemic illnesses or who are receiving concomitant drugs (see Section 4.2 DOSAGE AND METHOD OF ADMINISTRATION and Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE - Hyponatraemia).

Paediatric use (< 18 years)

The safety and efficacy of fluoxetine for the treatment of children and adolescents less than 18 years of age has not been established (see Section 4.6 FERTILITY, PREGNANCY AND LACTATION – Effects on fertility - Animal toxicology and Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)).

Effects on laboratory tests

No specific drug-laboratory interactions involving cross-reactivity of fluoxetine with assays for other substances (i.e., producing a false-positive or false-negative result) have been identified.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

As with all drugs, the potential for interaction by a variety of mechanisms (i.e., pharmacodynamic, pharmacokinetic drug inhibition or enhancement, etc.) is a possibility (see Section 5.2 PHARMACOKINETIC PROPERTIES - Accumulation and slow elimination).

Drugs metabolised by cytochrome P4502D6 (CYP2D6)

Approximately 3 to 10% of the normal population has reduced levels of activity of cytochrome P4502D6 (CYP2D6) as a result of a genetic defect. Such individuals have been referred to as "poor metabolisers" of drugs such as debrisoquine, dextromethorphan and tricyclic antidepressants. Many drugs, such as antipsychotic (e.g. phenothiazines and some atypical) and most antidepressants including fluoxetine and other selective uptake inhibitors of serotonin, are metabolised by this isoenzyme; thus, both the pharmacokinetic properties and relative proportion of metabolites are altered in poor metabolisers.

Like other agents that are metabolised by P4502D6 (CYP2D6), fluoxetine inhibits the activity of this isoenzyme and thus may make normal metabolisers resemble poor metabolisers. Treatment with medications that are predominantly metabolised by P4502D6 (CYP2D6) and that have a relatively narrow therapeutic index (e.g. flecainide, vinblastine, carbamazepine and tricyclic antidepressants) should be initiated at the low end of the dose range in patients currently taking fluoxetine or who have taken it in the preceding 5 weeks.

Tamoxifen has an important active metabolite, endoxifen, which is produced by CYP2D6 and contributes significantly to the efficacy of tamoxifen. Inhibition of CYP2D6 by fluoxetine leads to reduced plasma concentration of endoxifen (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE - Tamoxifen).

Drugs metabolised by cytochrome P4503A4

In vitro studies have shown ketoconazole, a potent inhibitor of cytochrome P4503A4 activity, to be at least 100 times more potent than fluoxetine or norfluoxetine as an inhibitor of the metabolism of several substrates for this enzyme, including astemizole, cisapride and midazolam. In an *in vivo* interaction study involving co-administration of fluoxetine with single doses of terfenadine (a cytochrome P4503A4 substrate), no increase in plasma terfenadine concentrations occurred with concomitant fluoxetine. No change in the pharmacokinetic profile or cognitive effect of midazolam 10 mg orally was observed, following a course of fluoxetine administration intended to produce steady state conditions, when compared with baseline determinations. These data indicate that fluoxetine's extent of inhibition of cytochrome P4503A4 activity is not likely to be of clinical significance.

Potential effects of co-administration of drugs highly bound to plasma proteins

Since fluoxetine is tightly bound to plasma protein, the concomitant use of fluoxetine with another highly protein bound drug (e.g. warfarin) may cause a shift in plasma concentrations of either drug, thus potentially resulting in an adverse effect. Conversely, adverse effects may result from displacement of protein bound fluoxetine by other tightly bound drugs (see Section 5.2 PHARMACOKINETIC PROPERTIES - Accumulation and slow elimination).

Tryptophan

Five patients receiving fluoxetine hydrochloride in combination with tryptophan experienced adverse reactions, including agitation, restlessness and gastrointestinal distress.

Warfarin

Altered anticoagulant 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 the concomitant use of warfarin with many other drugs, patients receiving warfarin therapy should receive careful coagulation monitoring when fluoxetine is initiated or stopped.

CNS active drugs

The risk of using fluoxetine in combination with other CNS active drugs has not been systematically evaluated. Data have been derived from circumstances which do not directly reflect the clinical setting. The clinical significance of in vitro and individual case report data is unknown. Nonetheless, caution is advised if the concomitant administration of fluoxetine and such drugs is required. In evaluating individual cases, consideration should be given to using lower initial doses of the concomitantly administered drugs, using conservative titration schedules, and monitoring of clinical status (see Section 5.2 PHARMACOKINETIC PROPERTIES - Accumulation and slow elimination).

Anticonvulsants. Patients receiving stable doses of phenytoin and carbamazepine have developed raised plasma anticonvulsant levels and clinical anticonvulsant toxicity following initiation of concomitant fluoxetine treatment.

Antipsychotics. Some evidence suggests a possible pharmacodynamic and/or pharmacokinetic interaction between some serotonin specific reuptake inhibitors (SSRIs) and some antipsychotics, including possible

elevation of blood levels of haloperidol and clozapine. Clinical studies of pimozide with other antidepressants demonstrate an increase in drug interaction or QTc prolongation. While a specific study with pimozide and fluoxetine has not been conducted, the potential for drug interactions or QTc prolongation warrants restricting the concurrent use of pimozide and fluoxetine. Concomitant use of fluoxetine and pimozide is contraindicated (see Section 4.3 CONTRAINDICATIONS).

Benzodiazepines. The half-life of concurrently administered diazepam may be prolonged in some patients and co-administration of alprazolam may result in increased plasma alprazolam concentrations.

Lithium. There have been reports of both increased and decreased lithium levels during combined therapy with fluoxetine and lithium. Cases of lithium toxicity and increased serotonergic effects have been reported. Lithium levels should be monitored when these drugs are administered concomitantly.

Serotonergic drugs. Co-administration with serotonergic drugs (e.g. SNRIs, SSRIs, tramadol or triptans such as sumatriptan) may result in serotonin syndrome.

Monoamine oxidase inhibitors. See Section 4.3 CONTRAINDICATIONS.

Other antidepressants. In two studies, previously stable plasma levels of imipramine and desipramine have increased greater than 2 to 10-fold when fluoxetine has been administered in combination. This influence may persist for three weeks or longer after fluoxetine is discontinued. Thus, the dose of tricyclic antidepressant (TCA) may need to be reduced and plasma TCA concentrations may need to be monitored temporarily when fluoxetine is co-administered or has been recently discontinued (see Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS - Drugs metabolised by cytochrome P4502D6 (CYP2D6)).

Metoprolol used in cardiac failure

Risk of metoprolol adverse events including excessive bradycardia, may be increased because of an inhibition of its metabolism by fluoxetine.

St John's Wort (Hypericum perforatum)

In common with other SSRI's, pharmacodynamic interactions between fluoxetine and the herbal remedy St John's Wort may occur, which may result in an increase of undesirable effects.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

Two fertility studies conducted in rats at dose levels of up to 9 - 12.5 mg/kg/day indicated that fluoxetine had no adverse effects on fertility. A slight decrease in neonatal survival was noted but this was probably associated with depressed maternal food consumption and suppressed weight gain.

Administration of fluoxetine to juvenile rats from weaning to young adulthood was associated with delayed sexual maturation, degenerative testicular and epididymal changes, and immaturity and inactivity of the female reproductive tract. Post-treatment assessment revealed reduced sperm concentrations and fertility, prolonged pairing-coitus interval, and histopathological changes indicative of irreversible seminiferous tubular degeneration and reversible epididymal vacuolation. These effects were observed at systemic exposures (plasma AUC) to fluoxetine and norfluoxetine of 5–20 fold higher than clinical paediatric exposure at a dose of 20 mg/day, and 2-7 fold higher than clinical paediatric exposure at 60 mg/day. At the no-effect level for these changes, exposure to fluoxetine and norfluoxetine was from less than clinical exposure to 8 fold higher than clinical exposure. The significance of these findings for human risk is unknown.

Animal toxicology - Phospholipids are increased in some tissues of mice, rats and dogs given fluoxetine chronically. This effect is reversible after cessation of fluoxetine treatment. Phospholipid accumulation in animals has been observed with many cationic amphiphilic drugs, including fenfluramine, imipramine and ranitidine. The significance of this effect in humans is unknown.

Administration of fluoxetine to juvenile rats from weaning to young adulthood was associated with growth retardation, skeletal muscle degeneration and adverse effects on male and female reproductive systems. Post treatment assessment revealed impaired nervous system function and adverse effects in reproductive parameters. These effects were observed at systemic exposures (plasma AUC) to fluoxetine and norfluoxetine of 5–20 fold higher than clinical paediatric exposure at a dose of 20 mg/day, and 2-7 fold higher than clinical paediatric exposure at 60 mg/day. At the no-effect level for these changes, exposure to fluoxetine and norfluoxetine was from less than clinical exposure to 8 fold higher than clinical exposure. The significance of these findings for human risk is unknown.

Use in pregnancy

Pregnancy Category: C

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.

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.

Transitory withdrawal symptoms 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.

Epidemiological studies have shown that the use of SSRI's in pregnancy, particularly use in late pregnancy, was associated with an increased risk of persistent pulmonary hypertension of 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.

Teratogenic effects - Reproduction studies have been performed in rats and rabbits at oral doses of up to 12.5 and 15 mg/kg/day respectively, and have revealed no evidence of harm to the fetus due to fluoxetine. However, there are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, fluoxetine should only be used during pregnancy if clearly required.

Labour and delivery - Observational data indicate an increased risk (less than 2 fold) of postpartum haemorrhage following SSRI/SNRI exposure within the month prior to birth.

Use in lactation

Fluoxetine and norfluoxetine are excreted in breast milk. Therefore, breastfeeding is not recommended during treatment with ZACTIN. The concentration of fluoxetine plus norfluoxetine was 70.4 nanogram/mL in one breast milk sample, while the mother's plasma concentration was 295.0 nanogram/mL. No adverse effects on the baby were reported. In another case, an infant breastfed by a mother on fluoxetine developed crying, sleep disturbance, vomiting and watery stools. The infant's plasma concentrations of fluoxetine and norfluoxetine on the second day of feeding were 340 nanogram/mL and 208 nanogram/mL, respectively.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

The effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration.

Interference with cognitive and motor performance

Patients should be cautioned about operating hazardous machinery or driving a car, until they are reasonably certain that fluoxetine does not affect them adversely.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

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.

Events observed during therapy with fluoxetine - clinical trials

The following events listed by body system have been observed. 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 1/10,000 patients. It is important to emphasise that, although the events reported did occur during treatment with fluoxetine, they were not necessarily caused by it.

Body as a whole - Very common: fatigue (including asthenia); Common: allergic reaction, chills; Uncommon: feeling abnormal; Rare: photosensitivity reaction, serum sickness; Very rare: anaphylactoid reaction, serotonin syndrome (neuroleptic malignant syndrome-like effects), mild intensity headache.

Cardiovascular system - Common: palpitations, vasodilatation; Uncommon: hypotension; Very rare: orthostatic hypotension.

Digestive system - Very common: diarrhoea, nausea; Common: anorexia, dyspepsia, gastrointestinal disorder, mouth dryness, vomiting; Uncommon: dysphagia; Rare: oesophageal pain.

Haemic and lymphatic systems - Uncommon: ecchymosis.

Metabolic and nutritional disorders - Common: weight loss.

Musculoskeletal system - Common: twitching.

Nervous system - Very common: anxiety, dizziness, headache, insomnia, nervousness, somnolence, tremor; Common: abnormal dreams, decreased libido, sleep disorder, abnormal thinking; Uncommon: akathisia, ataxia, balance disorder, bruxism, buccoglossal syndrome, depersonalisation, dyskinesia, manic reaction, myoclonus, seizures.

Respiratory system - Common: yawn.

Skin and appendages - Common: pruritus, rash, sweating, urticaria; Uncommon: alopecia.

Special senses - Common: abnormal vision, taste perversion; Uncommon: mydriasis.

Urogenital system - Common: abnormal ejaculation, gynaecological bleeding, impotence, urinary frequency; Uncommon: anorgasmia, breast pain, sexual dysfunction (occasionally persisting after treatment discontinuation), urination impaired; Rare: priaprism.

Investigations – Common: electrocardiogram data: QT interval prolongation (QTcF ≥450 msec).

Children and Adolescents - Common: epistaxis.

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. In addition, fluoxetine treatment was 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). The subjects grew more than their controls in observed-minus-expected BMI by 0.5 kg/m2 (95% CI: 0.0 to 1.0, p=0.0328). The mean additional change associated with fluoxetine treatment would amount to an extra 1.2 kg in a 152 cm tall person weighing 45 kg. 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 (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Spontaneous events

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 1/10,000 patients).

Body as a whole - Malignant hyperthermia, Stevens-Johnson syndrome, erythema multiforme.

Cardiovascular - Angioedema.

Digestive system - Abnormal hepatic function, aggravation of hepatic damage, hepatic failure/necrosis, idiosyncratic hepatitis, gastrointestinal bleeding[1].

Endocrine system - Inappropriate secretion of antidiuretic hormone.

Haemic and lymphatic systems - Eosinophilia, thrombocytopenic purpura.

Nervous system - Oculogyric crisis, tardive dyskinesia, memory impairment, confusion.

Skin and appendages - Epidermal necrolysis.

Urogenital system - Enlarged clitoris.

Reproduction system and breast disorders – Gynaecomastia, galactorrhoea, hyperprolactinaemia.

Musculoskeletal - Bone fractures.

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[1] Includes: oesophageal varices haemorrhage, gingival and mouth bleeding, haematemesis, haematochezia, haematomas [intra-abdominal, 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].

The following event have been reported for the therapeutic class of SSRIs/SNRIs (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE and Section 4.6 FERTILITY, PREGNANCY AND LACTATION):

Frequency "not known" - Postpartum haemorrhage

Discontinuation symptoms - 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.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

Symptoms

Cases of overdose of fluoxetine alone usually have an uncomplicated course and resolve without residual effects. 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. During a 13-year period, there were 34 fatal reports of overdose where fluoxetine was the only reported ingestant although many of the case reports were incomplete.

Management of overdose

Establish and maintain an airway; insure adequate oxygenation and ventilation. Activated charcoal, which may be used with sorbitol, should be considered in treating overdose. Activated charcoal may reduce absorption of the medicine if given within one or two hours after ingestion. In patients who are not fully conscious or have impaired gag reflex, consideration should be given to administering activated charcoal via a nasogastric tube, once the airway is protected.

Cardiac and vital signs monitoring is recommended, along with general symptomatic and supportive measures. Based on experience in animals, which may not be relevant to humans, fluoxetine-induced seizures which fail to remit spontaneously may respond to diazepam.

There are no specific antidotes for fluoxetine hydrochloride.

Due to the large volume of distribution of fluoxetine hydrochloride, forced diuresis, dialysis, haemoperfusion, and exchange transfusion are unlikely to be of benefit.

In managing overdosage, consider the possibility of multiple drug involvement. The physician should consider contacting the Poisons Information Centre on 13 11 26 for advice on the treatment of any overdosage.

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

The antidepressant and antiobsessional action of fluoxetine is presumed to be linked to its inhibition of CNS neuronal uptake of serotonin. Studies at clinically relevant doses in humans have demonstrated that fluoxetine blocks the uptake of serotonin, but not of noradrenaline, into human platelets. Animal studies also suggest that fluoxetine is a much more potent uptake inhibitor of serotonin than of noradrenaline.

Antagonism of muscarinic, histaminergic, and α_1-adrenergic receptors has been hypothesised to be associated with various anticholinergic, sedative, and cardiovascular effects of classical tricyclic antidepressant drugs. *In vitro*, fluoxetine binds to these and other membrane receptors from brain tissue much less potently than do the tricyclic antidepressants.

Clinical trials

Anxiety associated with major depression. A meta-analysis of randomised clinical trials provided acceptable evidence that (i) fluoxetine shows an efficacy at least equal to that of tricyclic antidepressants and is statistically significantly superior to placebo in the treatment of patients who have anxiety symptoms associated with a depressive illness, and (ii) the effect of fluoxetine is similar in depressed patients regardless of the presence or absence of associated anxiety.

Elderly. Fluoxetine has been studied in four clinical trials in elderly depressed patients (> 60 years of age). The efficacy shown by fluoxetine in these elderly patients was similar to its effects in younger adults. Fluoxetine was well tolerated by elderly depressed patients.

Maintenance of remission of depression. In a multicentre randomised double-blind continuation of those who were in remission after 12 weeks of open-label fluoxetine 20 mg/day, after 50 weeks (total duration) of fluoxetine 20 mg/day, the fluoxetine-treated patients had a statistically significantly lower rate of re-emergence of depressive symptoms than those on placebo. Although the numbers treated for 62 weeks were too few for efficacy evaluation, treatment with fluoxetine was safe and well-tolerated for this time.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

In humans, following a single oral 40 mg dose of fluoxetine, peak plasma concentrations from 15 to 55 nanogram/mL are observed after 6 to 8 hours. Fluoxetine is 80% to 95% absorbed following oral administration. There is a linear dose proportionality for the absorption of fluoxetine over the therapeutic dose range.

The systemic bioavailability of fluoxetine does not appear to be affected by food, although the absorption of fluoxetine may be slightly delayed. Thus, fluoxetine may be taken with or without food.

Distribution

The volume of distribution for fluoxetine is estimated at 30 to 40 L/kg.

Protein binding

Over the concentration range from 200 to 1,000 nanogram/mL, approximately 94.5% of fluoxetine is bound *in vitro* to human serum proteins including albumin and α-1-glycoprotein. The interaction between fluoxetine and other highly protein bound drugs has not been fully evaluated, but may be important (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Metabolism

Fluoxetine is extensively metabolised in the liver to norfluoxetine and a number of other unidentified metabolites. Norfluoxetine is the only identified active metabolite and is formed by demethylation of fluoxetine. In animal models, norfluoxetine's potency and selectivity as a serotonin uptake blocker are essentially equivalent to fluoxetine's.

Multiple cytochrome P450 isoenzymes, including CYP2D6, are responsible for the conversion of fluoxetine to norfluoxetine; thus other non-saturable oxidative pathways (i.e. non-2D6 pathways) contribute considerably to norfluoxetine formation (see Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

Excretion

The primary route of elimination appears to be hepatic metabolism to inactive metabolites which are excreted by the kidney.

Clinical issues related to metabolism/elimination

The complexity of the metabolism of fluoxetine has several consequences that may potentially affect fluoxetine's clinical use.

Accumulation and slow elimination

The relatively low elimination of fluoxetine (elimination half-life of 1 to 3 days after acute administration and 4 to 6 days after chronic administration) and its active metabolite, norfluoxetine (elimination half-life of 4 to 16 days after acute and chronic administration), leads to significant accumulation of the active species in chronic use. After 30 days of dosing at 40 mg/day, plasma concentrations of fluoxetine in the range of 91 to 302 nanogram/mL and norfluoxetine in the range of 72 to 258 nanogram/mL have been observed. The plasma concentrations of fluoxetine were higher than those predicted by single dose studies, presumably because fluoxetine's metabolism is not proportional to dose. Norfluoxetine, however, appears to have linear pharmacokinetics. Its mean terminal half-life after a single dose was 8.6 days and after multiple dosing was 9.3 days.

Thus, even if patients are given a fixed dose, steady state plasma concentrations are only achieved after weeks of continuous dosing. Nevertheless, the increase in plasma concentrations does not appear to be limitless. Specifically, patients taking fluoxetine at doses of 40 to 80 mg/day over periods as long as 3 years exhibited, on average, plasma concentrations similar to those seen among patients treated for 4 or 5 weeks.

Clinical issues related to accumulation and slow elimination

1. The long elimination half-lives of fluoxetine and norfluoxetine, the active drug substance will persist in the body for weeks even after treatment is ceased (primarily depending on individual patient characteristics, previous dosing regimen and length of previous therapy at discontinuation). This is of potential consequence when drug withdrawal is required or when drugs are prescribed that might interact with fluoxetine and norfluoxetine following the discontinuation of fluoxetine hydrochloride.

2. See Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE - The long elimination half-lives of fluoxetine and its metabolites.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Fluoxetine and norfluoxetine have been shown to have no genotoxic effects based on the following assays: bacterial mutation assay, DNA repair assay in cultured rat hepatocytes, and in vivo sister chromatid exchange assay in Chinese hamster bone marrow cells.

Carcinogenicity

There is no evidence of carcinogenicity with fluoxetine hydrochloride from animal studies. The dietary administration of fluoxetine to rats for two years at dose levels of 8 - 11 mg/kg/day produced no evidence of carcinogenicity.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

- lactose monohydrate
- maize starch

- colloidal anhydrous silica
- purified talc
- magnesium stearate
- brilliant blue FCF (CI 42090)
- quinoline yellow (CI 47005)
- indigo carmine (CI 73015)
- erythrosine (CI 45430)
- titanium dioxide
- sodium lauryl sulfate
- gelatin
- shellac
- propylene glycol
- ammonium hydroxide
- potassium hydroxide
- iron oxide black (CI 77499).

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25ºC.

6.5 NATURE AND CONTENTS OF CONTAINER

Container type: HDPE bottle or PVC/PVDC/Al blister packs

Pack sizes: 28’s

Some strengths, pack sizes and/or pack types may not be marketed..

Australian Register of Therapeutic Goods (ARTG)

AUST R 53773 - ZACTIN fluoxetine 20mg (as hydrochloride) capsule blister pack

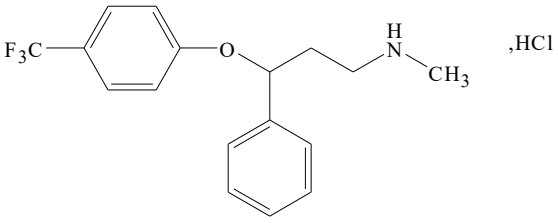
AUST R 53774 - ZACTIN fluoxetine 20mg (as hydrochloride) capsule bottle

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking it to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical Structure



Chemical name: (±)-N-methyl-3-phenyl-3-[(α,α,α-trifluoro-p-tolyl)-oxy]-propylamine hydrochloride

Molecular formula: $C_{17}H_{18}F_3NO.HCl$

Molecular weight: 345.79

Fluoxetine hydrochloride is a white to off-white crystalline solid with a solubility of 14 mg/mL in water.

CAS Number

54910-89-3

7 MEDICINE SCHEDULE (POISONS STANDARD)

S4 (Prescription Only Medicine)

8 SPONSOR

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Phone: 1800 274 276

9 DATE OF FIRST APPROVAL

13/11/1995

10 DATE OF REVISION

01/04/2026

Summary Table of Changes

Section Changed	Summary of New Information
All	Minor editorial changes
4.3	Addition of “Contraindication with metoprolol”
4.5	Addition of “Metoprolol used in cardiac failure”

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