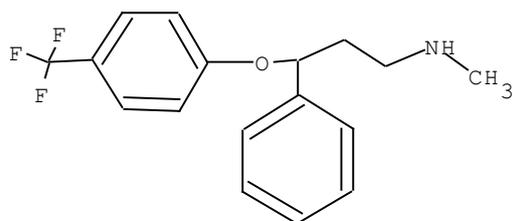

PRODUCT INFORMATION
FLUOXETINE SANDOZ 20 MG CAPSULES

NAME OF THE MEDICINE

Fluoxetine Hydrochloride , (R,S)-N-methyl-3-phenyl-3-[α,α,α -trifluoro-p-tolyl]-oxy]-propylamine hydrochloride.



. HCl

CAS [59333-67-4]

C₁₇H₁₈F₃NO.HCl

MW: 345.79

DESCRIPTION

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

Fluoxetine Sandoz capsules also contain pregelatinised maize starch, dimeticone 350, gelatin, titanium dioxide, yellow iron oxide CI 77492, and patent blue V CI42051.

PHARMACOLOGY

Pharmacodynamics

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. Studies in animals 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 classic tricyclic antidepressant drugs. Fluoxetine binds to these and other membrane receptors from brain tissue much less potently *in vitro* than do the tricyclic drugs.

Pharmacokinetics

Absorption

In humans, following a single oral 40 mg dose, peak plasma concentrations of fluoxetine 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. Food does not appear to affect the systemic bioavailability of fluoxetine, although it may delay its absorption inconsequentially. Thus fluoxetine may be administered with or without food.

Distribution

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

Protein binding

Over the concentration range from 200 to 1000 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 **PRECAUTIONS**).

Metabolism

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

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

Excretion

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

Clinical issues related to metabolism/elimination

The complexity of the metabolism of fluoxetine has several consequences, which may potentially affect its clinical use.

Accumulation and slow elimination

The relatively slow 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 these 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. Plasma concentrations of fluoxetine were higher than those predicted by single dose studies, presumably because its 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 continuous dosing for weeks. Nevertheless, plasma concentrations do not appear to increase without limit. Specifically, patients

receiving fluoxetine at doses of 40 to 80 mg/day over periods as long as a 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

The long elimination half-lives of fluoxetine and norfluoxetine ensure that, even when dosing is stopped, active drug substance will persist in the body for weeks, 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. For the clinical significance of the long elimination half lives of fluoxetine and its metabolites, see **PRECAUTIONS**.

CLINICAL TRIALS

Anxiety associated with major depression

A meta-analysis of randomised clinical trials provided acceptable evidence that fluoxetine shows an efficacy at least equal to that of tricyclic antidepressants and statistically significantly superior to placebo in the treatment of patients who have anxiety symptoms associated with depressive illness, and that 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 the elderly depressed patients (> 60 years of age). The efficacy shown by fluoxetine in these elderly patients was similar to effects in younger adults. Fluoxetine was well tolerated by elderly depressed patients.

Maintenance of remission of depression

In a multi-centre 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 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.

INDICATIONS

- Treatment of major depression.
- Treatment of obsessive compulsive disorder (OCD).

CONTRAINDICATIONS

Known hypersensitivity to fluoxetine hydrochloride or any of the other ingredients in the formulation.

Monoamine oxidase 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 fluctuation of vital signs and mental status changes that include extreme agitation progressing to delirium and coma.

Therefore, fluoxetine hydrochloride should not be used in combination with a MAOI (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 five weeks (perhaps longer, especially if fluoxetine has been prescribed chronically and/or at higher doses (see **PHARMACOLOGY**, Pharmacokinetics, 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 **PRECAUTIONS**).

Fluoxetine is contra-indicated in combination with metoprolol used in cardiac failure.

PRECAUTIONS

Rash and possibly allergic events

During premarketing testing of more than 5,600 US patients given fluoxetine, approximately 4% developed a rash and/or urticaria. Among these cases, almost a third 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, leucocytosis, arthralgias, oedema, carpal tunnel syndrome, respiratory distress, lymphadenopathy, proteinuria 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 known to have developed a serious cutaneous systemic illness. In neither patient was there an unequivocal diagnosis, but 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. Several other patients have had systemic syndromes suggestive of serum sickness.

Since the introduction of fluoxetine hydrochloride, 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 bronchospasm, angioedema and urticaria, alone and in combination, have been reported.

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

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

Anxiety and insomnia

Anxiety, nervousness and insomnia were reported by 10 to 15% of patients treated with fluoxetine hydrochloride. These symptoms led to drug discontinuation in 5% of patients treated with fluoxetine hydrochloride.

Altered appetite and weight

Significant weight loss, especially in underweight depressed patients, may be an undesirable result of treatment with fluoxetine hydrochloride. In controlled clinical trials, approximately 9% of patients treated with fluoxetine hydrochloride experienced anorexia. This incidence is approximately sixfold that seen in placebo controls. A weight loss of greater than 5% of bodyweight occurred in 13% of fluoxetine hydrochloride treated patients compared to 4% of placebo and 3% of tricyclic antidepressant treated patients. However, fluoxetine hydrochloride has only rarely been discontinued because of 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

During premarketing testing, hypomania or mania occurred in approximately 1% of fluoxetine treated patients. Activation of mania/hypomania has also been reported in a small proportion of patients with a major affective disorder treated with other marketed antidepressants.

Seizures

Twelve patients among more than 6,000 evaluated worldwide in the course of premarketing development of fluoxetine experienced convulsions (or events described as possibly having been seizures), a rate of 0.2%, which appears to be similar to that associated with other marketed antidepressants. Fluoxetine hydrochloride should be introduced with care in patients with a history of seizures.

Clinical worsening and suicide risk

The risk of suicide attempts 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 Sandoz 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 dosage 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 patients presenting symptoms. Patients (and caregivers of patients) should be alerted about the need to 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 comorbid depression associated with other psychiatric disorders being treated with antidepressants should be similarly observed for clinical worsening and suicidality.

Pooled analysis of 24 short-term (4 to 16 weeks) placebo-controlled trials of nine antidepressant medicines (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 almost 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 analysis included five SSRIs (citalopram, fluoxetine,

fluvoxamine, paroxetine, sertraline) and four non-SSRIs (bupropion, mirtazapine, nefazodone, venlafaxine).

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

Families and caregivers of children and adolescents being treated with antidepressants for major depressive disorder or for any other condition (psychiatric or non-psychiatric) 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 immediately to health care providers. 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 Sandoz should be written for the smallest quantity of tablets 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 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. hypokalemia or hypomagnesemia) or increased exposure to fluoxetine (e.g. hepatic impairment).

Long elimination half-lives

Because of the long elimination half-lives of the parent drug fluoxetine (1 to 3 days) and its major active metabolite norfluoxetine (4 to 16 days), changes in dose will not be fully reflected in plasma for several weeks, affecting both strategies for titration to final dose and withdrawal from treatment. (See **PHARMACOLOGY, Pharmacokinetics**, and **DOSAGE AND ADMINISTRATION**).

Withdrawal Reactions

Discontinuation symptoms have been reported in association with 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.

Hepatic impairment

See **DOSAGE AND ADMINISTRATION**.

Renal impairment

See **DOSAGE AND ADMINISTRATION**.

Use in patients with concomitant illness

Clinical trial experience with fluoxetine hydrochloride in patients with concomitant systemic illness is limited.

Caution is advisable in using fluoxetine hydrochloride in patients with diseases or conditions that could affect metabolism or haemodynamic responses.

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 those diagnoses were systematically excluded from clinical studies during premarket testing. However, the electrocardiograms of 312 patients who received fluoxetine hydrochloride in double blind trials were retrospectively evaluated; no conduction abnormalities that resulted in heart block were observed. The mean heart rate was reduced by approximately 3 beats/minute.

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

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.

In patients with diabetes, fluoxetine hydrochloride may alter glycaemic control. Hypoglycaemia has occurred during therapy with fluoxetine hydrochloride and hyperglycaemia has developed following discontinuation of the drug. As is true with many other types of medication when taken concurrently by patients with diabetes, insulin and/or oral hypoglycaemic dosage may need to be adjusted when therapy with fluoxetine hydrochloride is instituted or discontinued.

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 ADVERSE EFFECTS**). 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.

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 hydrochloride was discontinued. Although these cases were complex with varying possible aetiologies, some were possibly due to the syndrome of inappropriate antidiuretic hormone secretion (SIADH). The majority of these occurrences have been in older patients and in patients taking diuretics or who were otherwise volume depleted.

In a placebo controlled, double blind trial, ten of 313 fluoxetine patients and six of 320 placebo recipients had a lowering of 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 taking fluoxetine 20 mg daily. In five patients, hyponatraemia occurred within 19 days of commencement of fluoxetine, however fluoxetine withdrawal was associated with recovery in all cases. Hence, it may be advisable to monitor electrolytes in geriatric patients during the first 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.

Laboratory tests

No specific laboratory tests are recommended.

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.

Electroconvulsive therapy

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

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 **INTERACTIONS WITH OTHER MEDICINES**). 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.

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 (see Effects on Fertility). Post treatment assessment revealed impaired nervous system function and adverse effects in reproductive parameters (see Effects on Fertility). These effects were observed at systemic exposures (plasma AUC) to fluoxetine and norfluoxetine of 5-20 fold higher than clinical paediatric exposure of 20 mg/day and 2-7 fold higher than clinical paediatric exposure of 60 mg/day. At the no effect level for these changes, exposure to fluoxetine and norfluoxetine was less than clinical exposure to 8 fold higher than clinical exposure. The significance of these findings for human risk is unknown.

Drug abuse and 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 pre-marketing 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 history of drug abuse and follow such patients closely, observing them for signs of fluoxetine hydrochloride misuse or abuse (e.g. development of tolerance, incrementation of dose, drug seeking behaviour).

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.

Use in pregnancy

Australian Pregnancy Category C: Drugs which, owing to their pharmacological effects, have caused or may be suspected of causing, harmful effects on the human fetus or neonate without causing malformations.

These effects may be reversible. Accompanying texts should be consulted for further details.

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.

This drug crosses the placenta. 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 SSRIs (including fluoxetine) in pregnancy, particularly use in late pregnancy, was associated with an increased risk of persistent pulmonary hypertension of the newborn (PPHN). The risk of PPHN among infants born to women who used SSRIs late in pregnancy was estimated to be 4 to 5

times higher than the rate of 1 to 2 per 1000 pregnancies observed in the general population.

This potential risk should be weighed against the need for treatment during pregnancy.

Teratogenic effects

Reproduction studies have been performed in rats and rabbits at doses of up to 12.5 and 15 mg/kg/day and have revealed no evidence of harm to the foetus due to fluoxetine hydrochloride. There are, however, no adequate and well controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Labour and delivery

The effect of fluoxetine on labour and delivery in humans is unknown.

Use in lactation

Because fluoxetine is excreted in human milk, breastfeeding while on Fluoxetine Sandoz is not recommended. In one breast milk sample, the concentration of fluoxetine plus norfluoxetine was 70.4 nanogram/mL. The concentration in the maternal plasma was 295.0 nanogram/mL. No adverse effects on the infant were reported. In another case, an infant breast fed by a mother on fluoxetine treatment developed crying, sleep disturbance, vomiting and watery stools. The infant's plasma drug levels were fluoxetine 340 nanogram/mL and norfluoxetine 208 nanogram/mL on the second day of feeding.

Use in Children and Adolescents (< 18 years)

While clinical studies have been conducted in children and adolescents, the use of fluoxetine is not recommended in this population (see **PRECAUTIONS**, Clinical Worsening and Suicide Risk, Effects on Fertility, Animal Toxicology and **ADVERSE EFFECTS**).

Use in the elderly

Evaluation of patients over the age of 60 years who receive fluoxetine 20 mg daily revealed no unusual pattern of adverse events relative to clinical experience in younger patients. However, these data are insufficient to rule out possible age related differences during chronic use, particularly in elderly patients who have concomitant systemic illnesses or who are receiving concomitant drugs (see **PRECAUTIONS**, Hyponatraemia, and **DOSAGE AND ADMINISTRATION**).

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 of dose levels of 8-11 mg/kg/day produced no evidence of carcinogenicity.

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.

Interference with cognitive and motor performance

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

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, if they are breastfeeding an infant or if they develop a rash or hives.

INTERACTIONS WITH OTHER MEDICINES

As with all drugs, the potential for interaction by a variety of mechanisms (i.e. pharmacodynamic, pharmacokinetic drug inhibition or enhancement) is a possibility (see **PHARMACOLOGY**, Pharmacokinetics, Accumulation and slow elimination)

Drugs metabolised by cytochrome P450 3A4

In vitro studies have shown ketoconazole, a potent inhibitor of P450 3A4 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 10mg 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 P450 3A4 activity is not likely to be of clinical significance.

Drugs metabolised by cytochrome P450 2D6

Approximately 3 to 10% of the normal population has a genetic defect that leads to reduced levels of activity of cytochrome P450 2D6 (CYP 2D6). Such individuals have been referred to as poor metabolisers of drugs such as dextromethorphan and tricyclic antidepressants. Many drugs, such as 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.

Fluoxetine, like other agents that are metabolised by CYP 2D6, inhibits the activity of this isoenzyme and thus may make normal metabolisers resemble poor metabolisers. Therapy with medications that are predominantly metabolised by CYP 2D6 and that have a relatively narrow therapeutic index (e.g. flecainide, carbamazepine, vinblastine, tricyclic antidepressants) should be initiated at the low end of the dose range if a patient is taking fluoxetine concurrently or has taken it in the previous five 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 concentrations of endoxifen (see **PRECAUTIONS**).

Highly protein bound drugs

Because Fluoxetine Sandoz is tightly bound to plasma protein, the administration of fluoxetine to a patient taking another drug that is tightly bound to protein (e.g. warfarin) may cause a shift in plasma concentrations potentially resulting in an adverse effect. Conversely, adverse effects may result from displacement of protein bound fluoxetine by other tightly bound drugs (see **PHARMACOLOGY, Pharmacokinetics, 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 increase 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.

Central nervous system active drugs

The risk of using Fluoxetine Sandoz 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 Sandoz 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 **PHARMACOLOGY**).

Anticonvulsants

Patients on stable doses of phenytoin and carbamazepine have developed elevated plasma anticonvulsant concentrations and clinical anticonvulsant toxicity following initiation of concomitant fluoxetine treatment.

Antipsychotics

Some evidence suggests a possible pharmacodynamic and/or pharmacokinetic interaction between some 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 **CONTRAINDICATIONS**).

Benzodiazepines

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

Lithium

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

Serotonergic drugs

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

Monoamine oxidase inhibitors

(See **CONTRAINDICATIONS**).

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.

Mequitazine

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

Drugs that cause QT interval prolongation

Pharmacokinetic and pharmacodynamic studies between fluoxetine and other medicinal products that prolong the QT interval have not been performed. An additive effect of fluoxetine and these medicinal products cannot be excluded. Therefore, coadministration of fluoxetine with medicinal products that prolong the QT interval, should be used with caution.

Other antidepressants

In two studies, previously stable plasma levels of imipramine and desipramine have increased greater than two to ten times when fluoxetine has been administered in combination. This influence may persist for three weeks or longer after fluoxetine has been discontinued. Thus, the dose of tricyclic antidepressant may need to be reduced and plasma tricyclic antidepressant concentrations may need to be monitored temporarily when fluoxetine is coadministered or has been recently discontinued (see Drugs metabolised by CYP 2D6, above).

St John's wort

In common with other SSRIs, pharmacodynamic interactions between fluoxetine and the herbal remedy St John's wort (*Hypericum perforatum*) may occur, which may result in an increase of undesirable effects.

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 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).

ADVERSE EFFECTS

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

Associated with treatment discontinuation

15% of approximately 4,000 patients who received fluoxetine hydrochloride in US 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 patients treated with fluoxetine discontinued treatment early because of adverse events. Anxiety and rash at incidences of less than 2% were the most frequently reported events.

Incidence in clinical trials

The following events listed by body system have been observed. Very common adverse events are defined as those occurring on one or more occasions in at least 10% of patients; common adverse events are defined as those occurring on one or more occasions in at least 1% of patients; uncommon adverse events are those occurring in 0.1 to 1% of patients; rare events are those occurring in less than 0.1% of patients; very rare events are those occurring in less than 0.01% of 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 (includes asthenia)

Common: allergic reactions, 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/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(occasional persistence after treatment discontinuation), impaired urination

Rare: priapism

Children and Adolescents

Very common: headache

Common: epistaxis

Investigations

Common: Electrocardiogram Data: QT interval prolongation (QTcF \geq 450 msec)

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 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, $p=0.9673$). The subjects grew more than their controls in observed-minus-expected BMI by 0.5kg/m^2 (95% CI: 0.0 to 1.0, $p=0.328$). The mean additional change associated with fluoxetine treatment would amount to an extra 1.2kg in a 152cm tall person weighing 45kg. 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 **PRECAUTIONS**).

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 0.01% of patients).

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

Cardiovascular: Angioedema.

Digestive system: Aggravation of hepatic damage, abnormal hepatic function, hepatic failure/necrosis, idiosyncratic hepatitis, gastrointestinal bleeding¹.

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, galactorrhea, hyperprolactinemia.

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.

¹ Includes: esophageal varices hemorrhage, gingival and mouth bleeding, hematemesis, hematochezia, hematomas [intraabdominal, peritoneal], hemorrhage [anal, esophageal, gastric, gastrointestinal (upper and lower), haemorrhoidal, peritoneal, rectal], hemorrhagic diarrhoea and enterocolitis, hemorrhagic diverticulitis, hemorrhagic gastritis, melaena, and ulcer hemorrhage [esophageal, gastric, duodenal].

DOSAGE AND ADMINISTRATION

Depression

20 mg/day, administered in the morning, is the usual recommended initial dose.

If no clinical improvement is observed, a dose increase may be considered after several weeks. Doses above 20 mg/day should be administered on a b.i.d. schedule (i.e. morning and noon) and should not exceed a maximum dose of 80 mg/day. (See **PHARMACOLOGY, Pharmacokinetics, Accumulation and slow elimination.**)

As with other antidepressants, the full antidepressant effect may be delayed until four weeks of treatment or longer. (See **PHARMACOLOGY Pharmacokinetics, Accumulation and slow elimination**).

As with many other medications, a lower or less frequent dosage should be used in patients with hepatic impairment (see **PRECAUTIONS**). A lower or less frequent dosage should also be considered for patients, such as the elderly, with concurrent disease or on multiple medications (see **PRECAUTIONS**).

Obsessive compulsive disorder

Initial treatment

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 five 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) schedule. 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 obsessive compulsive disorder (OCD). The maximum fluoxetine dose should not exceed 80 mg/day.

A lower or less frequent dosage should be used in patients with hepatic impairment. A lower or less frequent dosage should also be considered for patients, such as the elderly, with concurrent disease or on multiple medications (see **PRECAUTIONS**).

Maintenance/continuation treatment

While there are no systematic studies that answer the question of how long to continue Fluoxetine Sandoz therapy, 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.

Age

Adjustment of dosage should not be required on the basis of age alone (see **PRECAUTIONS** for information on Hepatic impairment, Renal impairment, Use in

patients with concomitant illness and **INTERACTIONS WITH OTHER MEDICINES**).

Children and Adolescents (<18 years)

While clinical studies have been conducted in children and adolescents, the use of fluoxetine is not recommended in this population.

Liver disease

As might be predicted from its primary site of metabolism, hepatic impairment can affect the elimination of fluoxetine. The elimination half-life of fluoxetine was prolonged in a study of patients with cirrhosis, with a mean of 7.6 days compared to the range of two to three days seen in subjects without hepatic disease; norfluoxetine elimination was also delayed, with a mean duration of 12 days for patients with cirrhosis compared to the range of seven to nine days in normal subjects. This suggests that the use of Fluoxetine Sandoz in patients with hepatic disease must be approached with caution. If Fluoxetine Sandoz is administered to patients with hepatic disease, a lower or less frequent dose should be used (see **PRECAUTIONS, Impaired hepatic function**).

Renal disease

In depressed patients on dialysis (N=12), fluoxetine administered as 20mg 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.

OVERDOSAGE

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 ingested although many of the case reports were incomplete.

Management of overdose

Contact the Poisons Information Centre on 13 11 26 for advice on management of overdose.

In case of overdose treatment should be supportive and symptomatic.

Establish and maintain an airway; ensure adequate oxygenation and ventilation. Activated charcoal, which may be used with sorbitol, should be considered in treating

overdose. Cardiac and vital sign 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 that fail to remit spontaneously may respond to diazepam.

There are no specific antidotes for fluoxetine hydrochloride.

Because of 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.

PRESENTATION AND STORAGE CONDITIONS

Fluoxetine Sandoz 20 mg Capsules - Green capsules, available in blister packs of 28 capsules.

Storage conditions:

Store below 25°C.

NAME AND ADDRESS OF THE SPONSOR

Sandoz Pty Ltd
ABN 6007 5449 553
54 Waterloo Road
Macquarie Park, NSW 2113
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Tel: 1800 634 500

POISON SCHEDULE OF THE MEDICINE

Schedule 4 – Prescription only medicine

Date of first inclusion in the Australian Register of Therapeutic Goods (the ARTG): 09/06/1998

Date of most recent amendment: 22/12/2016