FLUOXETINE-GA 20 mg

PRODUCT INFORMATION

FLUOXETINE-GA (fluoxetine as hydrochloride) 20 mg Capsules

NAME OF THE MEDICINE

Fluoxetine-GA capsules contain fluoxetine hydrochloride, the chemical structure of which is represented below:

![Chemical Structure of Fluoxetine Hydrochloride]

The CAS number is 59333-67-4, with a molecular formula of C₁₇H₁₈F₃NO.HCl and a molecular weight of 345.79.

The chemical name of fluoxetine hydrochloride is (±)-N-methyl-3-phenyl-3-[(α,α,α-trifluoro-p-tolyl)-oxy]-propylamine hydrochloride.

DESCRIPTION

Fluoxetine hydrochloride is a white or almost white crystalline powder. It is freely soluble in methanol and ethanol; soluble in acetonitrile, chloroform and acetone; slightly soluble in ethyl acetate, dichloromethane and water.

Fluoxetine-GA is available in 20 mg capsules. Each capsule contains fluoxetine 20 mg, as fluoxetine hydrochloride and the following excipients: lactose, Cellulose-microcrystalline, magnesium stearate, Silica-colloidal anhydrous, gelatin, titanium dioxide CI77891, iron oxide yellow CI77492, quinoline yellow CI47005 and indigo carmine CI73015.

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 α₁-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 less potently in vitro than do the tricyclic drugs.
Pharmacokinetics

Systemic bioavailability
In humans, following a single oral 40 mg dose, peak plasma concentrations of fluoxetine from 15 to 55 nanogram/mL are observed after six to eight hours. Fluoxetine-GA 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 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 α1-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 drugs).

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 fluoxetine’s clinical use.

Accumulation and slow elimination
The relatively slow elimination of fluoxetine (elimination half-life of one to three days after acute administration and four to six days after chronic administration) and its active metabolite, norfluoxetine (elimination half-life of four 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 three years exhibited, on average, plasma concentrations similar to those seen among patients treated for four or five weeks.

Clinical issues related to accumulation and slow elimination
The long elimination half-lives of fluoxetine and norfluoxetine assure 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 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 tricyclic antidepressants and statistically significantly superior to placebo in 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 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 significant lower rate 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

**CONTRAINDICATIONS**

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

*Pimozide*
Concomitant use in patients taking pimozide is contraindicated (see PRECAUTIONS).

*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 hyperthermia, rigidity, clonus, myoclonus, tremor, shivering, hyperreflexia, autonomic instability with possible rapid fluctuations 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 an 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 an MAOI. Limited reports suggest that orally administered cyproheptadine or intravenously administered dantrolene may benefit patients experiencing such reactions. Animal studies also suggest that cyproheptadine may be beneficial.

PRECAUTIONS

Rash and possibly allergic events
During pre-marketing 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 alternative aetiology cannot be identified, fluoxetine 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 six times 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.
**Activation of mania/hypomania**
During premarket 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 major affective disorder treated with other marketed antidepressants.

**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 antidepressants with little or no CYP2D6 inhibition.

**Seizures**
Twelve patients among more than 6,000 evaluated worldwide in the course of premarket 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 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. The risk must be considered in all depressed patients.

Although a causal role for Fluoxetine-GA 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 patients presenting symptoms. Patients (and caregivers of patients) should be alerted about the need to monitor for any worsening of their condition and/or 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 analysis of 24 short-term (4 to 16 weeks) placebo-controlled trials of nine antidepressants 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 most consistently observed in the major depressive disorder trials but there were signals of risk arising from the trials in other psychiatric indications (obsessive compulsive disorder and social anxiety disorder) as well. No suicides occurred in these trials. It is unknown whether the suicidality risk in children and adolescent patients extends to use beyond several months. The nine antidepressant medicines in the pooled analyses included five SSRIs (citalopram, fluoxetine, fluvoxamine, paroxetine, sertraline) and four non-SSRIs (bupropion, mirtazapine, nefazodone, venlafaxine).

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

Families and caregivers of children and adolescents being treated with antidepressants for major depressive disorder or for any other condition (psychiatric or 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-GA should be written for the smallest quantity of capsules consistent with good patient management, in order to reduce the risk of overdose.

**Long elimination half-lives of fluoxetine and its metabolites**

Because of the long elimination half-lives of the parent drug fluoxetine (one to three days) and its major active metabolite norfluoxetine (four 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 selective serotonin reuptake inhibitors (SSRIs). Because of the long elimination half-life of fluoxetine, and its active metabolite norfluoxetine, plasma fluoxetine and norfluoxetine concentrations decrease gradually at the conclusion of therapy, which reduces greatly the likelihood of developing discontinuation symptoms and makes dosage tapering unnecessary in most patients.

Common symptoms associated with withdrawal of SSRIs include dizziness, paraesthesia, headache, anxiety and nausea. Onset of symptoms can occur within a day of discontinuation but may be delayed, particularly in the case of fluoxetine, due to its long half-life. The majority of symptoms experienced on withdrawal of SSRIs are non serious, self-limiting and have varying durations. Fluoxetine has been only rarely associated with such symptoms.

**Concomitant illness**

Clinical trial experience with fluoxetine hydrochloride in patients with concomitant systemic illness is limited. Caution is advisable in using fluoxetine 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 these diagnoses were systematically excluded from clinical studies during the pre-market testing of fluoxetine. 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 is instituted or discontinued. (See also Impaired renal function and Impaired hepatic function).

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). The majority of these occurrences have been in older patients and in patients taking diuretics or who was 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 elderly 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.

Electroconvulsive therapy
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.

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 at a dose of 20 mg/day and a 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.

Impaired renal function (see DOSAGE AND ADMINISTRATION)

Impaired hepatic function (see DOSAGE AND ADMINISTRATION)

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).

Carcinogenesis
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.

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.

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 (Category C)
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 SSRI's (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 SSRI’s late in pregnancy was estimated to be 5 times higher the rate of 1 to 2 per 1000 pregnancies observed in the general population.

**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 fetus 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 is not recommended. In one breast milk sample, the concentration of fluoxetine plus norfluoxetine was 70.4 nanogram/mL. The concentration in the mother's plasma was 295.0 nanogram/mL. No adverse effects on the infant 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 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)**
The safety and efficacy of fluoxetine for the treatment of children and adolescents less than 18 years of age has not been established (see Effects on Fertility, Animal Toxicology and ADVERSE EFFECTS).

**Effect on ability to drive or operate machinery**
Patients should be cautioned about operating hazardous machinery or driving a car until they are reasonably certain that treatment with fluoxetine does not affect them adversely.

**Instructions to patients**
Doctors are advised to discuss the following issues with patients for whom they prescribe fluoxetine. Because fluoxetine hydrochloride may impair judgement, thinking or motor skills, patients should be advised to avoid driving a car or operating hazardous machinery until they are reasonably certain that their performance is not affected.

Patients should be advised to inform their doctor if they are taking or plan to take any prescription or over-the-counter drugs or alcohol.

Patients should be advised to notify their doctor if they become pregnant or intend to become pregnant during therapy, if they are breastfeeding 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 2D6*

Approximately 3 to 10% of the normal population has a genetic defect that leads 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 and 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).

*Drugs metabolised by cytochrome P450 3A4*

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

*Highly plasma protein bound drugs*

Because fluoxetine 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 increased bleeding, have been reported uncommonly when fluoxetine is co-administrated 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 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 PHARMACOLOGY- Accumulation and Slow Elimination).

**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**

Co-administration with serotonergic drugs (e.g. SNRIs, SSRIs, tramadol, sumatriptan) may lead to an increase of 5-HT-associated effects.

**Monoamine oxidase inhibitors.** See CONTRAINDICATIONS.

**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).

**Hypericum perforatum (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.

**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.

**Drug abuse and Dependence**

**Physical and psychological dependence**

Fluoxetine hydrochloride has not been systemically 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, doctors should carefully evaluate patients for a history of drug abuse and follow the progress of such patients closely, observing them for signs of fluoxetine misuse or abuse (e.g. development of tolerance, incrementation of dose or drug seeking behaviour).

**ADVERSE EFFECTS**

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

**Children and Adolescents (<18 years)**  
Very Common: Headache

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 1.1cm less in height (p=0.004) and 1.1kg less in weight (p=0.008) than subjects treated with placebo. In addition, fluoxetine treatment was associated with decrease in alkaline phosphatase levels. There are no studies that directly evaluate the longer-term effects of fluoxetine on the growth, development and maturation of children and adolescent patients. Therefore, height and weight should be monitored periodically in paediatric patients receiving fluoxetine (see PRECAUTIONS).

**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: asthenia
Common: allergic reactions, chills
Rare: photosensitivity reaction, serum sickness
Very rare: anaphylactoid reaction, serotonin syndrome (neuroleptic malignant syndrome-like effects), mild intensity headache

**Cardiovascular**

Common: palpitations, vasodilatation
Very rare: orthostatic hypotension
Gastrointestinal
Very common: diarrhoea, nausea
Common: anorexia, dyspepsia, gastrointestinal disorder, mouth dryness, vomiting
Uncommon: dysphagia

Haematological
Uncommon: ecchymosis

Metabolic/nutritional
Common: weight loss

Musculoskeletal
Common: twitching

Neurological
Very common: anxiety, dizziness, insomnia, nervousness, somnolence, tremor
Common: abnormal dreams, decreased libido, sleep disorder, abnormal thinking
Uncommon: akathisia, ataxia, buccoglossal syndrome, depersonalisation, manic reaction, myoclonus, convulsions

Respiratory
Common: yawn

Dermatological
Common: pruritus, rash, sweating, urticaria
Uncommon: alopecia

Special senses
Common: abnormal vision, taste perversion
Uncommon: mydriasis

Genitourinary
Common: abnormal ejaculation, impotence, urinary frequency
Uncommon: anorgasmia, breast pain, impaired urination
Rare: priapism

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

Gastrointestinal
Aggravation of hepatic damage, abnormal hepatic function, hepatic failure/necrosis, idiosyncratic hepatitis

Endocrine
Inappropriate secretion of antidiuretic hormone

Haematological
Eosinophilia, thrombocytopenic purpura
Neurological
Oculogyric crisis, tardive dyskinesia

Dermatological
Epidermal necrolysis

Genitourinary
Enlarged clitoris, gynaecomastia

**DOSAGE AND ADMINISTRATION**

**General**

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

If no clinical improvement is observed after several weeks, a dose increase may be considered. Doses above 20 mg/day should be administered twice daily (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 elderly patients and patients 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 after several weeks, a dose increase may be considered. 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 daily (morning) or twice daily (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 dose should be used in patients with hepatic impairment. A lower or less frequent dosage should also be considered for elderly patients and patients 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 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.

**General**

**Impaired hepatic function**
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 in patients with hepatic disease must be approached with caution. If fluoxetine is administered to patients with hepatic disease, a lower or less frequent dose should be used (See PRECAUTIONS).

**Impaired renal function**
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 PRECAUTIONS for information on Concomitant illness, Impaired renal function, Impaired hepatic function and Interactions with other Medicines).

**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.

**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 to cardiac arrest, 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; ensure adequate oxygenation and ventilation. Activated charcoal, which may be used with sorbitol, should be considered in treating overdose.

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 overdose, consider the possibility of multiple drug involvement. The physician should consider contacting a Poisons Information Centre (Telephone no: 13 11 26) for advice on the treatment and management of any overdosage.
PRESENTATION AND STORAGE CONDITIONS

Fluoxetine-GA 20 mg capsules are a size 3 gelatin capsule with an opaque light green cap and an opaque ivory body, containing a white, odourless powder. They are available in blister pack of 28 capsules. Store below 25°C

NAME AND ADDRESS OF THE SPONSOR

Ascent Pharma Pty Ltd
151-153 Clarendon St
South Melbourne Vic. 3205

www.ascentpharma.com.au

FLUOXETINE-GA fluoxetine hydrochloride 20mg capsule blister pack, AUSTR 148090

POISON SCHEDULE OF THE MEDICINE

S4

DATE OF TGA APPROVAL

11th April 2008

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