1.3.1.1 Professional Information for Medicines for Human Use

SCHEDULING STATUS

S5

1. NAME OF THE MEDICINE

GENOFINEX 20 mg Capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

GENOFINEX 20 mg Capsules:

Each capsule contains fluoxetine hydrochloride equivalent to 20 mg fluoxetine

Sugar free

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

GENOFINEX 20 mg Capsules:

Opaque green cap/opaque off-white body, size '3' hard gelatine capsule filled with white to off-white granular powder and imprinted with 'E' on opaque green cap and '91' on opaque off-white body with black ink

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

GENOFINEX is indicated for the treatment of major depressive episodes: i.e. single episode and recurrent depression with associated anxiety.

GENOFINEX is used in the treatment of Bulimia nervosa where it has been shown to significantly decrease binge-eating and purging activity.

GENOFINEX is used in the treatment of Obsessive-compulsive disorder. The obsessions or compulsions must be experienced as intrusive, markedly distressing, time consuming or interfering significantly with the person's social or occupational functioning.
4.2. Posology and method of administration
Posology
A major depressive episode Adults and elderly: A dose of 20 mg/day is recommended, preferably in the morning.
Bulimia nervosa A dose of 60 mg/day is recommended.
Obsessive-compulsive disorder A dose of 20 to 60 mg/day is the recommended dose for the treatment of obsessive-compulsive disorder.
The recommended dose may be increased or decreased. Doses above 80 mg/day are not recommended for any indication. Upward dose titration is advised at intervals of several weeks due to the kinetic properties of GENOFINEX (see section 5.2).
Elderly GENOFINEX should be used with caution in all elderly patients, particularly if they have systemic illness or are receiving multiple medications for concomitant diseases. Dosages over 20 mg per day are not recommended (see section 5.2).
Concurrent disease A lower or less frequent dose should be considered in patients with hepatic impairment and concurrent diseases.
Discontinuation of fluoxetine

Discontinuation of GENOFINEX may lead to withdrawal symptoms, including dizziness, paraesthesia, headache, insomnia, tremor, confusion, sensory disturbances, agitation, anxiety and nausea (see sections 4.4 and 4.8)

Abrupt discontinuation should be avoided. When stopping treatment with fluoxetine, the dose should be gradually reduced over a period of at least one to two weeks in order to reduce the risk of withdrawal reactions (see section 4.4 and section 4.8). If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, then resuming the previously prescribed dose may be considered. Subsequently, the medical practitioner may continue decreasing the dose, but at a more gradual rate.

Method of administration

GENOFINEX may be administered with or without food. The capsules may be swallowed whole or be dispersed in approximately 100 ml water.

4.3. Contraindications

GENOFINEX is contraindicated:

- In patients with hypersensitivity to fluoxetine or to any excipients in GENOFINEX (see section 6.1).
- In children under the age of 18 years, as the safety and efficacy of GENOFINEX has not been established
- And should not be administered to patients with severe renal failure (GFR <10 ml/min) because accumulation may occur in these patients during chronic treatment.
- **In concomitant use with Monoamine oxidase inhibitors** (see section 4.5)
- **In concomitant use with Thioridazine** (see section 4.5)

4.4. Special warnings and precautions for use

Patients with major depressive disorder, both adults and children, may experience worsening of their depression and/or the emergence of suicidal ideation and behaviour, whether or not they are taking antidepressant medicines. This risk may persist until significant remission occurs.

The safety and efficacy of GENOFINEX have not been established in children under the age of 18 years. In clinical trials in Major Depressive Disorder, there were increased reports of hostility and suicide-related adverse events such as suicidal ideation and self-harm. (See (see section 4.3)

Suicide

Isolated cases of suicidal ideation and suicidal behaviours have been reported during GENOFINEX therapy or early after treatment discontinuation. Although a causal role for GENOFINEX alone in inducing such behaviours has not been established, pooled analyses from studies of some other antidepressants in psychiatric conditions indicate a potential increased risk for suicidal ideation and suicidal behaviours in paediatric patients compared to placebo.

Patients being treated with GENOFINEX should be observed closely for clinical worsening and suicidality, especially at the beginning of a course of therapy or at any time of dose changes, either increases or decreases.

Medical Practitioners should encourage patients of all ages to report any distressing thoughts or feelings at any time.

Because of the possibility of comorbidity between major depressive disorder and other psychiatric and non-psychiatric disorders, the same precautions should be observed when treating patients with major depressive disorder when treating patients with other psychiatric and non-psychiatric disorders.

The following symptoms have been reported in patients being treated with antidepressants for major depressive disorder as well as for other indications, both psychiatric and non-psychiatric: anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia, hypomania and mania. Although a causal link between the emergence of such symptoms and either the worsening of depression and/or the emergence of suicidal impulses has not been established, consideration should be given to changing the therapeutic regimen, including possibly discontinuing GENOFINEX in patients for whom such symptoms are severe, abrupt in onset or were not part of the patient's presenting symptoms.

If the decision is made to discontinue treatment, GENOFINEX should be tapered (see section 4.2)

Serotonin syndrome

A serotonin syndrome, which may be confused with neuroleptic malignant syndrome, may occur with the use of GENOFINEX . This syndrome is characterised by the clustering of clinical features of changes in mental state (confusion, disorientation, agitation) and neuromuscular activity (myoclonus, hyper-reflexia, tremor, rigidity, inco-ordination), in combination with auto-immune dysfunction (especially fever, sweating, diarrhoea). The serotonin syndrome has been seen in temporal association with the use of monoamine oxidase inhibitors and with other serotonergic medication, but may occur in the absence of any concomitant medication. GENOFINEX should be stopped immediately as serious morbidity and death may follow the serotonin syndrome.

Rash and possibly allergic events

Rash, anaphylactoid events and progressive systemic events, sometimes serious and involving skin, kidney, liver or lung, have been reported in patients taking GENOFINEX . Upon the appearance of rash or of other possibly allergic phenomena, GENOFINEX should be discontinued.

Seizures

GENOFINEX should be introduced cautiously in patients who have a history of seizures. GENOFINEX should be discontinued in any patient who develops seizures. GENOFINEX should be avoided in patients with unstable epilepsy; patients with controlled epilepsy should be carefully monitored.

There have been reports of prolonged seizures in patients on GENOFINEX receiving ECT treatment (see section 4.5)

Fluoxetine as in GENOFINEX is extensively metabolised by the liver and excreted by the kidneys. A lower dose, e.g. alternate day dosing, is recommended in patients with significant hepatic dysfunction or mild to moderate renal failure (GFR 10-50 ml/min).
Clinical experience in acute cardiac disease is limited, therefore caution is advisable. Fluoxetine as in GENOFINEX is should not be used in combination with metoprolol used in cardiac failure (see section 4.5).
GENOFINEX may cause loss of mass which could be undesirable in underweight depressed patients.
In patients with diabetes, GENOFINEX may alter glycaemic control. Hypoglycaemia has occurred during therapy with fluoxetine and hyperglycaemia has developed following discontinuation. Insulin and/or oral hypoglycaemic dosage may need to be adjusted when GENOFINEX therapy is initiated or discontinued.
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 GENOFINEX had a causative role.
Although GENOFINEX has been shown not to affect psychomotor performance in healthy volunteers, any psychoactive medicine may impair judgement, thinking or motor skills. Therefore, patients should be cautioned that their ability to perform potentially hazardous tasks (e.g. driving a motor vehicle or operating machinery) may be impaired.
As improvement may not occur during the first two or more weeks of treatment, patients should be closely monitored during this period. Due to the risk of suicide in major depressive episodes, close supervision of high risk patients should accompany medication therapy.

Because of well-established comorbidity between obsessive-compulsive disorder and depression, the same precautions observed when treating patients with depression should be observed when treating patients with obsessive-compulsive disorder.
There have been reports of extrapyramidal symptoms associated with the use of GENOFINEX and of aggravation of Parkinson's disease in patients taking GENOFINEX . GENOFINEX should therefore be used with care in patients with extrapyramidal disorders.
Discontinuation of GENOFINEX may lead to withdrawal symptoms, including dizziness, paraesthesia, headache, insomnia, tremor, confusion, sensory disturbances, agitation, anxiety and nausea (see section 4.2).
Abnormal bleeding SNRIs and SSRIs, including fluoxetine as in GENOFINEX , may increase the risk of bleeding reactions. Concomitant use of aspirin, nonsteroidal anti-inflammatory drugs, warfarin, and other anti-coagulants may add to this risk. Case reports and epidemiological studies (case-control and cohort design) have demonstrated an association between use of medicines that interfere with serotonin reuptake and the occurrence of gastrointestinal bleeding. Bleeding reactions related to SNRIs and SSRIs use have ranged from ecchymoses, hematomas, epistaxis, and petechiae to life-threatening haemorrhages. Patients should be cautioned about the risk of bleeding associated with the concomitant use of GENOFINEX and NSAIDs, aspirin, warfarin, or other medicines that affect coagulation (see section 4.5)
Angle-Closure Glaucoma The pupillary dilation that occurs following use of many antidepressant medicines including fluoxetine as in GENOFINEX may trigger an angle closure attack in a patient with anatomically narrow angles who does not have a patent iridectomy.

Hyponatremia

Hyponatremia has been reported during treatment with SNRIs and SSRIs, including fluoxetine as in GENOFINEX . In many cases, this hyponatremia appears to be the result of the syndrome of inappropriate antidiuretic hormone secretion (SIADH). Cases with serum sodium lower than 110 mmol/L have been reported and appeared to be reversible when fluoxetine as in GENOFINEX was discontinued. Elderly patients may be at greater risk of developing hyponatremia with SNRIs and SSRIs. Also, patients taking diuretics or who are otherwise volume depleted may be at greater risk. Discontinuation of GENOFINEX should be considered in patients with symptomatic hyponatremia and appropriate medical intervention should be instituted.

Signs and symptoms of hyponatremia include headache, difficulty concentrating, memory impairment, confusion, weakness, and unsteadiness, which may lead to falls. More severe and/or acute cases have been associated with hallucination, syncope, seizure, coma, respiratory arrest, and death.

QT Prolongation

Post-marketing cases of QT interval prolongation and ventricular dysrhythmia including Torsades de Pointes have been reported in patients treated with fluoxetine as in GENOFINEX . GENOFINEX should be used with caution in patients with congenital long QT syndrome; a previous history of QT prolongation; a family history of long QT syndrome or sudden cardiac death; and other conditions that predispose to QT prolongation and ventricular dysrhythmia. Such conditions include concomitant use of medicine that prolong the QT interval; hypokalemia or hypomagnesemia; recent myocardial infarction, uncompensated heart failure, bradydysrhythmias, and other significant dysrhythmias; and conditions that predispose to increased fluoxetine exposure (overdose, hepatic impairment, use of CYP2D6 inhibitors,

CYP2D6 poor metaboliser status, or use of other highly protein-bound drugs). Fluoxetine as in GENOFINEX is primarily metabolised by CYP2D6 (see sections 4.3, 4.5, 4.8 and 5.1) Thioridazine is contraindicated for use with GENOFINEX (see section 4.3) and pimozide should not be used with GENOFINEX (see section 4.5). Avoid the concomitant use of medicines known to prolong the QT interval. These include specific antipsychotics (e.g., ziprasidone, iloperidone, chlorpromazine, mesoridazine, droperidol,); specific antibiotics (e.g., erythromycin, gatifloxacin, moxifloxacin, sparfloxacin); Class 1A antidysrhythmic medications (e.g., quinidine, procainamide); Class III antidysrhythmics (e.g., amiodarone, sotalol); and others (e.g., pentamidine, levomethadyl acetate, methadone, halofantrine, mefloquine, dolasetron mesylate, probucol or tacrolimus)

Consider ECG assessment and periodic ECG monitoring if initiating treatment with GENOFINEX in patients with risk factors for QT prolongation and ventricular dysrhythmia. Consider discontinuing GENOFINEX and obtaining a cardiac evaluation if patients develop signs or symptoms consistent with ventricular dysrhythmia.

4.5. Interaction with other medicines and other forms of interaction

Medicines metabolised by cytochrome P450IID6 isoenzyme

Because GENOFINEX has the potential to inhibit the cytochrome P450IID6 isoenzyme, therapy with medications that are predominantly metabolised by the P450IID6 system and that have a relatively narrow therapeutic index should be initiated at the low end of the dose range if a patient is receiving GENOFINEX concurrently or has taken it in the previous 5 weeks. If GENOFINEX is added to the treatment regimen of a patient already receiving such a medicine, the need for decreased dose of the original medication should be considered.

Do not give GENOFINEX together with metoprolol when it is used in cardiac failure. The risk of metoprolol adverse events, including excessive bradycardia, may be increased, because of an inhibition of its metabolism by fluoxetine (see section 4.4).

Monoamine oxidase inhibitors

There have been reports of serious, sometimes fatal, reactions (including hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs and mental status changes that include extreme agitation progressing to delirium and coma) in patients receiving GENOFINEX in combination with a monoamine oxidase inhibitor (MAOI) and in patients who have recently discontinued GENOFINEX and are then started on an MAOI. Some cases presented with features resembling neuroleptic malignant syndrome. Therefore, GENOFINEX should not be used in combination with an MAOI, or within 14 days of discontinuing therapy with an MAOI. Since GENOFINEX and its major metabolite have very long elimination half-lives, at least 5 weeks should be allowed after stopping GENOFINEX before starting an MAOI. If GENOFINEX has been prescribed chronically and/or at a high dose, a longer interval should be considered. Serious and fatal cases of serotonin syndrome (which may resemble and be diagnosed as neuroleptic malignant syndrome) have been reported in patients treated with GENOFINEX and an MAOI in temporal proximity (see section 4.4).

CNS active medicines

Caution is advised if the concomitant administration of GENOFINEX and CNS active medicine, including lithium, is required. There have been reports of both increased and decreased lithium levels when used concomitantly with fluoxetine as in GENOFINEX .

Serotonergic Medicines

Concomitant use of other medicines with serotonergic activity (e.g. Serotonin and Norepinephrine Reuptake Inhibitors, Selective Serotonin Reuptake Inhibitors, triptans or tramadol) may result in serotonin syndrome. (see section 4.4)

There have been greater than 2-fold increases of previously stable plasma levels of other antidepressants when GENOFINEX has been administered in combination with these medicines.

Patients receiving GENOFINEX in combination with tryptophan have been reported to experience adverse reactions, including agitation, restlessness and gastrointestinal distress.

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

Pimozide

Patients taking pimozide should not take GENOFINEX concomitantly. Pimozide can prolong the QT interval. Fluoxetine as in GENOFINEX can increase the level of pimozide through inhibition of CYP2D6. Fluoxetine can also prolong the QT interval. Clinical studies of pimozide with other antidepressants demonstrate an increase in interaction or QT prolongation. While a specific study with pimozide and fluoxetine has not been conducted, the potential for interactions or QT prolongation warrants restricting the concurrent use of pimozide and GENOFINEX .

Thioridazine

Thioridazine should not be administered with GENOFINEX or within a minimum of 5 weeks after GENOFINEX has been discontinued. Thioridazine administration produces a dose

related prolongation of the QTc interval which is associated with serious ventricular dysrythmias, such as torsades de pointes - type dysrythmias and sudden death. This risk is expected to increase with fluoxetine-induced inhibition of thioridazine metabolism.
Tricyclic Antidepressants (TCAs) In 2 studies, previously stable plasma levels of imipramine and desipramine have increased greater than 2- to 10-fold when fluoxetine has been administered in combination. This influence may persist for 3 weeks or longer after GENOFINEX is discontinued. Thus, the dose of TCAs may need to be reduced and plasma TCA concentrations may need to be monitored temporarily when GENOFINEX is co-administered or has been recently discontinued (see section 4.4 and 5.1)
Benzodiazepines The half-life of concurrently administered diazepam may be prolonged in some patients. Co-administration of alprazolam and fluoxetine as in GENOFINEX has resulted in increased alprazolam plasma concentrations and in further psychomotor performance decrement due to increased alprazolam levels.
The half-life of concurrently administered diazepam may be prolonged.
Antipsychotics Some clinical data suggests a possible pharmacodynamic and/or pharmacokinetic interaction between SSRIs and antipsychotics. Elevation of blood levels of haloperidol and clozapine has been observed in patients receiving concomitant fluoxetine as in GENOFINEX .
Anticoagulants 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 as in GENOFINEX is co-administered with warfarin. As is prudent in concomitant

use of warfarin with many other medicines, patients receiving warfarin therapy should receive careful coagulation monitoring when GENOFINEX is initiated or stopped.

Serotonin

Serotonin release by platelets plays an important role in haemostasis. Epidemiological studies of the case-control and cohort design that have demonstrated an association between use of psychotropic medicines that interfere with serotonin reuptake and the occurrence of upper gastrointestinal bleeding have also shown that concurrent use of an NSAID or aspirin may potentiate this risk of bleeding. Altered anticoagulant effects, including increased bleeding, have been reported when SNRIs or SSRIs are co-administered with warfarin. Patients receiving warfarin therapy should be carefully monitored when fluoxetine GENOFINEX therapy is initiated or discontinued (see section 4.4)

The long elimination half-lives of fluoxetine and its active metabolite should be borne in mind (see 'Pharmacokinetics') when considering pharmacodynamic or pharmacokinetic medicine interactions, or the potential consequence when medicines are prescribed that might interact with either substance following the discontinuation of GENOFINEX .

Fluoxetine as in GENOFINEX is bound to plasma protein and concurrent administration may alter plasma concentrations of other plasma protein bound medicines, e.g. warfarin, digitoxin, or conversely, fluoxetine binding may be changed by other medicines. There have been reports of prolonged seizures in patients on GENOFINEX receiving ECT treatment (see section 4.4)

Medicines Metabolised by CYP3A4

In an in vivo interaction study involving co- administration of GENOFINEX with single doses of terfenadine (a CYP3A4 substrate), no increase in plasma terfenadine concentrations occurred with concomitant fluoxetine as in GENOFINEX .

Additionally, in vitro studies have shown ketoconazole, a potent inhibitor of CYP3A4 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. These data indicate that fluoxetine's extent of inhibition of CYP3A4 activity is not likely to be of clinical significance.

Olanzapine

Fluoxetine as in GENOFINEX (60 mg single dose or 60 mg daily dose for 8 days) causes a small (mean 16%) increase in the maximum concentration of olanzapine and a small (mean 16%) decrease in olanzapine clearance. The magnitude of the impact of this factor is small in comparison to the overall variability between individuals, and therefore dose modification is not routinely recommended.

4.6. Fertility, pregnancy and lactation

Safety of use of **GENOFINEX** during pregnancy and lactation has not been established

Pregnancy

GENOFINEX is not recommended to be used in pregnancy, due to the potential risk to the foetus. After administration of fluoxetine late in pregnancy, the following effects have been reported in neonates: irritability, tremor, hypotonia, persistent crying, and difficulty in sucking or in sleeping. These symptoms may indicate either serotonergic effects or a withdrawal syndrome.

Epidemiological data have suggested that the use of SSRIs in late pregnancy, may increase the risk of persistent pulmonary hypertension in the newborn (PPHN).

Abrupt discontinuation of therapy should be avoided during pregnancy (see Section 4.2).

Lactation

The safety of GENOFINEX has not been established in breastfeeding women.

Fertility:

Animal data have shown that fluoxetine may affect sperm quality. Human case reports with some SSRIs have shown that an effect on sperm quality is reversible.

Impact on human fertility has not been observed so far

4.7. Effects on ability to drive and use machines

Although GENOFINEX has been shown not to affect psychomotor performance in healthy volunteers, any psychoactive medicine may impair judgement, thinking or motor skills. Therefore, patients should be advised to avoid driving a car or operating hazardous machinery until they are certain that their performance is not affected.

4.8. Undesirable effects

a. *Summary of the safety profile*

The most commonly reported adverse reaction are chest pain, chills, haemorrhage, hypertension and palpitations. Adverse reactions affecting the digestive system include increased appetite, nausea and vomiting. Weight gain is also a commonly reported adverse reaction. Common adverse reaction affecting the nervous system include agitation, amnesia, confusion, emotional lability and sleep disorder. Ear pain, taste perversion and tinnitus were common reported adverse reaction affecting the senses. Increase in urinary frequency has also been reported.

b. *Tabulated list of adverse reactions*

System organ class	**Frequent (≥1/100 to <1/10)**	**Less frequent (≥1/1000 to <1/100)**

Blood and lymphatic system disorders		Anaemia, ecchymosis, Blood dyscrasia, hypochromic anaemia, leucopenia, lymphoedema, lymphocytosis, petechia, purpura, thrombocythaemia, thrombocytopenia
Endocrine System		Hypothyroidism, Diabetic acidosis, diabetes mellitus
Metabolism and nutrition disorders	Weight gain	Dehydration, generalised oedema, gout, hypercholesteraemia, hyperlipaemia, hypokalaemia, peripheral oedema, Alcohol intolerance, alkaline phosphatase increased, BUN increased, creatine phosphokinase increased, hyperkalaemia, hyperuricaemia, hypocalcaemia, iron deficiency anaemia, ALT increased

Nervous System Disorders	Agitation, amnesia, confusion, emotional lability, sleep disorder	Abnormal gait, acute brain syndrome, akathisia, apathy, ataxia, buccoglossal syndrome, CNS depression, CNS stimulation, depersonalisation, euphoria, hallucinations, hostility, hyperkinesia, hypertonia, hypesthesia, incoordination, libido increased, myoclonus, neuralgia, neuropathy, neurosis, paranoid reaction, personality disorder 2, psychosis, vertigo, Abnormal electroencephalogram, antisocial reaction, circumoral paraesthaesia, coma, delusions, dysarthria, dystonia, extrapyramidal syndrome, foot drop, hyperaesthesia, neuritis, paralysis, reflexes decreased, reflexes increased, stupor
Eye Disorders		Conjunctivitis, dry eyes, mydriasis, photophobia, Blepharitis, diplopia,

		exophthalmos, eye haemorrhage, glaucoma, iritis, scleritis, strabismus, visual field defect
Ear and labyrinth disorders	Ear pain, tinnitus	Deafness, hyperacusis, parosmia
Cardiac Disorders	Haemorrhage, hypertension, palpitation	Angina pectoris, dysrhythmiathmia, congestive heart failure, hypotension, migraine, myocardial infarct, postural hypotension, syncope, tachycardia, vascular headache, Atrial fibrillation, bradycardia, cerebral embolism, cerebral ischaemia, cerebrovascular accident, extrasystoles, heart arrest, heart block, pallor, peripheral vascular disorder, phlebitis, shock, thrombophlebitis, thrombosis, vasospasm, ventricular dysrhythmiathmia, ventricular extrasystoles, ventricular fibrillation
Respiratory, thoracic and mediastinal disorders		Asthma, epistaxis, hiccup, hyperventilation, Apnoea, atelectasis, cough decreased, emphysema, haemoptysis, hypoventilation, hypoxia,

		larynx oedema, lung oedema, pneumothorax, stridor
Gastrointestinal disorders	Increased appetite, nausea and vomiting	Aphthous stomatitis, cholelithiasis, colitis, dysphagia, eructation, oesophagitis, gastritis, gastroenteritis, glossitis, gum haemorrhage, hyperchlorhydria, increased salivation, liver function tests abnormal, melena, mouth ulceration, nausea/ vomiting/diarrhoea, stomach ulcer, stomatitis, thirst, Biliary pain, bloody diarrhoea, cholecystitis, duodenal ulcer, enteritis, oesophageal ulcer, faecal incontinence, gastrointestinal haemorrhage, hematemesis, haemorrhage of colon, hepatitis, intestinal obstruction, liver fatty deposit, pancreatitis, peptic ulcer, rectal haemorrhage, salivary gland enlargement, stomach ulcer haemorrhage, tongue oedema
Skin and subcutaneous tissue disorders		Acne, alopecia, contact dermatitis, eczema, maculopapular rash, skin discolouration, skin ulcer,vesiculobullous rash, Furunculosis, herpes zoster,

		hirsutism, petechial rash, psoriasis, purpuric rash, pustular rash, seborrhoea
Musculoskeletal and connective tissue disorders		Arthritis, bone pain, bursitis, leg cramps, tenosynovitis, Arthrosis, chondrodystrophy, myasthenia, myopathy, myositis, osteomyelitis, osteoporosis, rheumatoid arthritis
Renal and urinary disorders	Urinary frequency increased	Abortion, albuminuria, amenorrhoea, anorgasmia, breast enlargement, breast pain, cystitis, dysuria, female lactation, fibrocystic breast, haematuria, leucorrhoea, menorrhagia, metrorrhagia, nocturia, polyuria, urinary incontinence, urinary retention, urinary urgency, vaginal haemorrhage, Breast engorgement, glycosuria, hypomenorrhoea, kidney pain, oliguria, priapism, uterine haemorrhage, uterine fibroids enlarged
General disorders and administrative site conditions	Chest pain, chills	Chills and fever, face oedema, intentional overdose, malaise, pelvic pain, suicide attempt, Acute abdominal syndrome, hypothermia, intentional injury, neuroleptic malignant syndrome, photosensitivity reaction

c. Description of selected adverse reactions

Suicide/suicidal thoughts or clinical worsening:

Cases of suicidal ideation and suicidal behaviour have been reported during fluoxetine therapy or early after treatment discontinuation (see section 4.4).

In paediatric clinical trials suicide-related behaviours (suicide attempt and suicidal thoughts), hostility, and self-harm have been reported.

Seizures

There have been reports of prolonged seizures in patients on GENOFINEX receiving ECT treatment (see section 4.5)

Withdrawal symptoms seen on discontinuation of SSRI treatment

Discontinuation of fluoxetine as in GENOFINEX (particularly when abrupt) commonly leads to withdrawal symptoms. Dizziness, sensory disturbances (including paraesthesia), sleep disturbances (including insomnia and intense dreams), asthenia, agitation or anxiety, nausea and/or vomiting, tremor and headache are the most commonly reported reactions. It is therefore advised that when GENOFINEX treatment is no longer required, gradual discontinuation by dose tapering should be carried out (see section 4.2).

Clinical experience in acute cardiac disease is limited, therefore caution is advisable (See section 4.5)

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions to SAHPRA via the '6.04 Adverse Drug Reactions Reporting Form'. Found under SAHPRA's publications: https://www/sahpra.org.za/Publications/Index/8

4.9. Overdose

Symptoms

Symptoms of overdose included nausea, vomiting, seizures, cardiovascular dysfunction ranging from asymptomatic dysrhythmias to cardiac arrest, pulmonary dysfunction and signs of altered CNS status ranging from excitation to coma.

Treatment

Cardiac and vital signs monitoring is recommended along with general symptomatic and supportive measures.

There are no specific antidotes for GENOFINEX .

Due to the large volume of distribution of GENOFINEX , forced diuresis, dialysis, haemoperfusion and exchange transfusion are unlikely to be of benefit. In managing overdosage, the possibility of multiple drug involvement should be considered.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

A1.2 Psychoanaleptics (antidepressants)

Mechanism of action

Although the exact mechanism of fluoxetine is unknown, its antidepressant and anti-obsessive-compulsive action is presumed to be linked to its inhibition of CNS neuronal uptake of serotonin.

5.2. Pharmacokinetic properties

Absorption

Fluoxetine is well absorbed after oral administration.

Food does not appear to affect the systemic bioavailability of fluoxetine, although it may delay its absorption by 1 to 2 hours, which is probably not clinically significant. Thus, fluoxetine may be administered with or without food.

Distribution

Peak plasma concentration is reached in 6 to 8 hours after a single dose of 40 mg. Because of the long elimination half-lives of the parent drug (4 to 6 days) and its major active metabolite, norfluoxetine (4 to 16 days), changes in dose will not be fully reflected in plasma for several weeks (approximately 4 half-lives). This is to be taken into consideration during dose titration or cessation of treatment. Fluoxetine is extensively bound to plasma proteins (about 95%) and is widely distributed (volume of distribution: 2- 40L/kg). Steady-state plasma concentrations are achieved after dosing for several weeks

Biotransformation

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, Fluoxetine is a racemic mixture (50/50) of R-fluoxetine and S-fluoxetine enantiomers. In animal models, both enantiomers are specific and potent serotonin uptake inhibitors with essentially equivalent pharmacologic activity. The S-fluoxetine enantiomer is eliminated more slowly and it is the predominant enantiomer present in plasma at steady state.

S-norfluoxetine is a potent and selective inhibitor of serotonin uptake and has activity essentially equivalent to R- or S-fluoxetine. R-norfluoxetine is significantly less potent than the parent drug in the inhibition of serotonin uptake. The primary route of elimination appears to be hepatic metabolism to inactive metabolites excreted by the kidney.

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 actives in chronic use and delayed attainment of steady state, even when a fixed dose is used. After 30 days of dosing at 40 mg/day, plasma concentrations of fluoxetine in the range of 91 to 302 ng/mL and norfluoxetine in the range of 72 to 258 ng/mL have been observed. Plasma concentrations of fluoxetine were higher than those predicted by single-dose studies, because fluoxetine's metabolism is not proportional to dose. Norfluoxetine, however, appears to have linear pharmacokinetics. Its mean terminal half-life after a single dose was 8.6 days and after multiple dosing was 9.3 days.

The long elimination half-lives of fluoxetine and norfluoxetine assure that, even when dosing is stopped, active medicine 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 medicine titration or discontinuation is required or when medicines are prescribed that might interact with fluoxetine and norfluoxetine following the discontinuation of fluoxetine.

Linearity

Steady-state levels after prolonged dosing are similar to levels seen at 4 to 5 weeks.

Special Populations

Liver disease

As might be predicted from its primary site of metabolism, liver impairment can affect the elimination of fluoxetine. The elimination half-life of fluoxetine was prolonged in a study of cirrhotic patients, with a mean of 7.6 days compared with the range of 2 to 3 days seen in subjects without liver disease; norfluoxetine elimination was also delayed, with a mean duration of 12 days for cirrhotic patients compared with the range of 7 to 9 days in normal subjects. This

suggests that the use of fluoxetine in patients with liver disease must be approached with caution. If fluoxetine is administered to patients with liver disease, a lower or less frequent dose should be used

Renal disease

In depressed patients on dialysis (N=12), fluoxetine administered as 20 mg once daily for 2 months produced steady-state fluoxetine and norfluoxetine plasma concentrations comparable with 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.

Elderly patients

The disposition of single doses of fluoxetine in healthy elderly subjects (>65 years of age) did not differ significantly from that in younger normal subjects. However, given the long half-life and nonlinear disposition of the medicine, a single-dose study is not adequate to rule out the possibility of altered pharmacokinetics in the elderly, particularly if they have systemic illness or are receiving multiple medicines for concomitant diseases. The effects of age upon the metabolism of fluoxetine have been investigated in 260 elderly but otherwise healthy depressed patients (≥60 years of age) who received 20 mg fluoxetine for 6 weeks. Combined fluoxetine plus norfluoxetine plasma concentrations were 209.3 ± 85.7 ng/mL at the end of 6 weeks. No unusual age-associated pattern of adverse reactions was observed in those elderly patients.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Colloidal silicon dioxide and pregelantinised starch

Composition of capsule shell:

FD&C Blue 1, gelatin, sodium lauryl sulphate, titanium dioxide, yellow iron oxide

Composition of Ink:

Black iron oxide, butyl alcohol, dehydrated alcohol, isopropyl alcohol, potassium hydroxide, propylene glycol, purified water, shellac, strong ammonia solution

6.2. Incompatibilities

Not applicable

6.3. Shelf life

3 years

6.4. Special precautions for storage

Store at or below 25 °C.

Keep in original packaging until required for use.

KEEP OUT OF REACH OF CHILDREN.

6.5. Nature and contents of container

30 capsules are packed in clear PVC/PVDC aluminium foil blister pack. Each carton contains 3 blisters of 10 capsules each. The blisters are further packed in preprinted cartons with leaflet

30 capsules are packed in white opaque round HDPE container closed with a white opaque polypropylene stock ribbed closure with wad having induction dealing liner. The HDPE containers are further packed in preprinted cartons with leaflet

Not all packs and pack sizes are necessarily marketed.

6.6. Special precautions for disposal of a used medicine or waste materials derived from such medicine and other handling of the product

No special requirements.

7. NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION

Aurogen South Africa (Pty) Ltd

Woodhill Office Park, Building 1

53 Phillip Engelbrecht Avenue

Meyersdal, Ext. 12, 1448

Johannesburg

South Africa

8. REGISTRATION NUMBER

47/1.2/0075

9. DATE OF FIRST AUTHORISATION

26 JAN 2021