NEW ZEALAND DATA SHEET

LUVOX

1. Product Name

Luvox, 50 mg and 100 mg, Film coated tablet.

2. Qualitative and Quantitative Composition

Each film coated tablet contains 50 mg or 100 mg of fluvoxamine maleate.

For the full list of excipients, see section 6.1.

3. Pharmaceutical Form

Luvox 50 mg – round, biconvex, scored white film-coated tablets inscribed on one side of the tablet with '291' on either side of the score.

Luvox 100 mg – oval, biconvex, scored white film-coated tablets inscribed on one side of the tablet with '313' on either side of the score.

4. Clinical Particulars

4.1 Therapeutic indications

Luvox is indicated for the treatment of depressive illness and the symptoms of depressive disorder, and for the treatment of the symptoms of obsessive compulsive disorders (OCD).

4.2 Dose and method of administration

Dose

Depression

The recommended starting dose of fluvoxamine is 50 mg per day, given as a single dose in the evening. Doses should be gradually increased until an effective dose is reached, with a maximum of 300 mg per day. The usually effective dose is 100 mg per day. Doses up to 150 mg can be given as a single dose. It is recommended that total daily doses of greater than 150 mg be given in 2 or 3 divided doses.

In agreement with the consensus statement of the WHO, antidepressant medication should be continued for at least 6 months after recovery from a depressive episode.

Obsessive compulsive disorder

The recommended starting dose of fluvoxamine is 50 mg per day for 3 to 4 days. The dosage should be increased gradually until an effective dose is achieved, with a maximum of 300 mg per day. The usually effective dose is in the range of 100-300 mg/day. Doses up to 150 mg per day can be given as a single dose, preferably in the evening. It is recommended that a total daily dose of more than 150mg is given in 2 or 3 divided doses.

If a good therapeutic response is achieved, treatment can be continued at the required dosage. There are no systematic studies which address the issue of the length of treatment. However, since obsessive compulsive disorder (OCD) is a chronic condition, it is reasonable to consider continuation beyond 10 weeks in responding patients. Dosage adjustments should be made carefully, on an individual patient basis, throughout therapy to maintain the patient at the lowest effect dose. The need for treatment should be reassessed periodically. Some clinicians advocate concomitant behavioural psychotherapy for patients who have responded well on pharmacotherapy.

If no improvement is observed within 10 weeks of initiation of therapy, treatment with fluvoxamine should be reconsidered.

Method of administration

Luvox tablets should be swallowed with water, without chewing.

Withdrawal symptoms seen on discontinuation of fluvoxamine

Abrupt discontinuation should be avoided. When stopping treatment with fluvoxamine, the dose should be gradually reduced over a period of at least one or two weeks in order to reduce the risk of withdrawal reactions (see sections 4.4 and 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 physician may continue decreasing the dose, but at a more gradual rate.

4.3 Contraindications

Luvox is contraindicated in patients with hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Luvox tablets are contraindicated in combination with tizanidine and monoamine oxidase inhibitors (MAOIs) (see section 4.5). Treatment with fluvoxamine can be initiated:

- two weeks after discontinuation of an irreversible MAOI, or
- the following day after discontinuation of a reversible MAOI (e.g. moclobemide, linezolid).

At least one week should elapse between discontinuation of fluvoxamine and initiation of therapy with any MAOI.

Fluvoxamine immediate release tablets should not be used in combination with ramelteon

4.4 Special warnings and precautions for use

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 a risk for bipolar disorder; such screening should include a detailed psychiatric history, including a family history of suicide, bipolar disorder and depression.

Clinical worsening and suicide risk associated with psychiatric disorders

The risk of suicide attempt is inherent in depression and may persist until significant remission occurs. This risk must be considered in all depressed patients.

Patients with depression may experience worsening of their depressive symptoms and/or the emergence of suicidal ideation and behaviours (suicidality) whether or not they are taking antidepressant medications, and this risk may persist until significant remission occurs. As improvement may not occur during the first few weeks or more of treatment, patients should be closely monitored for clinical worsening and suicidality, especially at the beginning of a course of treatment, or at the time of dose changes, either increases or decreases. Consideration should be

given to changing the therapeutic regimen, including possibly discontinuing the medication, in patients whose depression is persistently worse or whose emergent suicidality is severe, abrupt in onset, or was not part of the patient's presenting symptoms.

Patients (and caregivers of patients) should be alerted about the need to 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. Patients with co-morbid depression associated with other psychiatric disorders being treated with antidepressants should be similarly observed for clinical worsening and suicidality.

Obsessive compulsive disorders may also be associated with an increased risk of suicide-related events. The same precautions should therefore be observed for these patients.

Patients with a history of suicide-related events, or those exhibiting a significant degree of suicidal ideation prior to commencement of treatment, are at a greater risk of suicidal thoughts or suicide attempts, and should receive careful monitoring during treatment.

Pooled analyses 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 most consistently observed in the major depressive disorder trials, but there were signals of risk arising from trials in other psychiatric indications (obsessive compulsive disorder and social anxiety disorder) as well. No suicides occurred in these trials. It is unknown whether the suicidality risk in children and adolescent patients extends to use beyond several months. The nine antidepressant medicines in the pooled analyses included five SSRIs (citalopram, fluoxetine, fluvoxamine, paroxetine, sertraline) and four non-SSRIs (buproprion, mirtazapine, nefazodone, venlafaxine).

Pooled analysis of short term studies of antidepressant medications have also shown an increased risk of suicidality in young adults aged 18 to 24 during initial treatment (generally the first one to two months). Short term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond the age of 24 years; there was a reduction with antidepressants compared to placebo in adults aged 65 years and older.

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

Akathisia/psychomotor restlessness

The use of fluvoxamine has been associated with the development of akathisia. This is most likely to occur within the first few weeks of treatment. In patients who develop these symptoms, increasing the dose may be detrimental.

The presentation of akathisia may be variable and comprises subjective complaints of restlessness and an overwhelming urge to move and either distress or motor phenomena such as pacing, swinging of the legs while seated, rocking from foot to foot, or both. Particular attention should be paid to the monitoring for such symptoms and signs as, left untreated, akathisia is associated with poor compliance and an increased risk of relapse.

Nervous system disorders

Reversible cerebral vasoconstriction syndrome (thunderclap headache) has been associated with serotonergic agents such as SSRIs or triptans. Although in animal studies, fluvoxamine has non pro-convulsive properties, caution is recommended when this medicine is administered to patients with a history of convulsive disorders. Fluvoxamine should be avoided in patients with unstable epilepsy and patients with controlled epilepsy should be carefully monitored. Treatment with fluvoxamine should be discontinued if seizures occur or if seizure frequency increases.

Metabolism and nutrition disorders

As with other SSRIs, hyponatraemia has been rarely reported, and appears to be reversible when fluvoxamine is discontinued. Some cases were possibly due to the syndrome of inappropriate antidiuretic hormone secretion. The majority of reports were associated with older patients.

Glycaemic control may be disturbed (i.e., hyperglycaemia, hypoglycaemia, decreased glucose tolerance), especially in the early stages of treatment. When fluvoxamine is given to patients with a known history of diabetes mellitus, the dosage of anti-diabetic drugs may need to be adjusted.

Eye disorders

Mydriasis has been reported in association with SSRIs such as fluvoxamine. Therefore caution is recommended when prescribing fluvoxamine for patients with raised intraocular pressure or those at risk of acute narrow-angle glaucoma.

Haematological disorders

There have been reports of cutaneous bleeding abnormalities such as ecchymoses and purpura as well as other haemorrhagic manifestations such as gastrointestinal bleeding or gynaecological haemorrhage with SSRIs. Caution is advised in patients taking SSRIs, particularly in elderly patients and in patients who concomitantly use drugs known to affect platelet function (e.g. atypical antipsychotics and phenothiazines, most tricyclic antidepressants, aspirin and NSAIDs) or drugs that increase risk of bleeding as well as in patients with a history of bleeding disorders and in those with predisposing conditions (e.g. thrombocytopenia, or coagulation disorders). If any significant bleeding or bruising is observed, it is recommended that a platelet count should be performed.

Cardiac disorders

Cases of QTc prolongation and Torsades de Pointes (TdP), have been reported during the post-marketing use of fluvoxamine. The majority of reports occurred in patients with other risk factors for QTc prolongation/TdP.

Therefore, fluvoxamine should be used with caution in patients with risk factors for QTc prolongation including congenital long QT syndrome, age>65 years, female sex, structural heart disease/LV dysfunction, medical conditions such as renal or hepatic disease, use of medicines that inhibit the metabolism of fluvoxamine, and the concomitant use of other QTc prolonging medicines (see section 4.5).

Hypokalaemia and hypomagnesaemia should be corrected prior to treatment.

In high risk patients, an ECG should be performed prior to starting treatment, at steady state, after dose increases or after starting any potentially interacting medicine. Electrolytes should be monitored periodically and any abnormalities should be corrected prior to starting fluvoxamine. An ECG should also be performed in all patients experiencing symptoms that could be indicative of an arrhythmia (e.g. dizziness, palpitations, syncope or new onset seizures).

Consideration should be given to stopping fluvoxamine treatment or reducing the dose if the QTc interval is >500ms or increases by >60ms.

When combined with fluvoxamine plasma concentrations of terfenadine, astemizole or cisapride may be increased resulting in an increased risk for QT-prolongation/Torsade de Pointes. Therefore fluvoxamine should not be co-administered with these agents.

Fluvoxamine may cause an insignificant decrease in heartbeat (2-6 beats per minute).

Electroconvulsive therapy (ECT)

There is limited clinical experience of concomitant administration of fluvoxamine and ECT; therefore caution is advisable.

Serotonin syndrome

Development of serotonin syndrome or neuroleptic malignant syndrome-like events may occur in association with treatment with SSRIs, particularly when given in combination with MAOIs or other serotonergic and/or neuroleptic agents. Symptoms and signs of serotonin syndrome include rapid onset of neuromuscular excitation (hyperreflexia, incoordination, myoclonus, tremor), altered mental status (confusion, irritability, extreme agitation progressing to delirium and coma, hypomania) and autonomic dysfunction (diaphoresis, diarrhoea, fever, shivering and rapidly fluctuating vital signs).

Treatment with fluvoxamine should be discontinued if such events occur and supportive symptomatic treatment initiated.

Mania/hypomania

Fluvoxamine should be used with caution in patients with a history of mania/hypomania. Fluvoxamine should be discontinued in any patient entering a manic phase.

Discontinuation/withdrawal symptoms (see also section 4.2)

The onset of symptoms may occur one to three days after abrupt discontinuation of SSRI therapy and (rarely) after dosage lowering. It is important but may be difficult to distinguish the discontinuation symptoms from a recurrence of the underlying disease. Both may present with disturbances of the equilibrium and of the sensory system. However, they may differ in view of the severity, onset and duration of the symptoms.

Discontinuation symptoms rarely occur after treatment of less than 5 weeks duration and usually last from one day to three weeks.

The most commonly reported symptoms in association with withdrawal of the medicine include: dizziness, sensory disturbances (including paraesthesia, visual disturbances and electric shock sensations), sleep disturbances (including insomnia and intense dreams), agitation, irritability, confusion, emotional stability, headache, nausea and/or vomiting, diarrhoea, sweating, palpitations, tremor and anxiety (see section 4.8). Generally, these effects are mild to moderate and are self-limiting; however in some patients they may be severe and/or prolonged. They usually occur within the first few days of discontinuing treatment.

It is advised that in accordance with clinical experience and individual need of a patient the dosage should be gradually tapered over a couple of weeks when discontinuing treatment (see section 4.2).

Elderly

Data in elderly subjects give no indication of clinically significant differences in pharmacokinetics compared with younger subjects. Nevertheless, upward dose titration should be carried out more slowly in this patient population, and dosing should always be handled with caution.

Paediatric

Fluvoxamine should not be used in children and adolescents (age <18 years) for the treatment of major depressive disorder as the efficacy and safety of the medicine in these patients for this condition has not been satisfactorily investigated. Suicide-related behaviours (suicide attempt and suicidal thoughts), and hostility (predominantly aggression, oppositional behaviour and anger) were more frequently observed in clinical trials among children and adolescents treated with antidepressants compared to those treated with placebo. If based on clinical need, a decision to treat is taken; the patient should be carefully monitored for the appearance of suicidal symptoms.

Decreased appetite and weight loss have been observed in association with the use of fluvoxamine as well as with other SSRIs. Although no detrimental effect on growth, development and maturation was apparent in the long-term, open-label clinical studies in children, regular monitoring of weight and growth is recommended if treatment of a child with an SSRI is to be continued long term.

Use in renal insufficiency

Patients suffering from renal insufficiency should start on a low dose and be carefully monitored when treated with fluvoxamine. Upward dose titration should be carried out more slowly in this patient population.

Use in hepatic insufficiency

Patients suffering from hepatic insufficiency should start on a low dose and be carefully monitored when treated with fluvoxamine. Upward dose titration should be carried out more slowly in this patient population.

Clearance of fluvoxamine is slower in patients with hepatic impairment (e.g. cirrhosis).

Treatment with fluvoxamine has rarely been associated with an increase in hepatic enzymes, generally accompanied by clinical symptoms. In such cases treatment should be discontinued.

Effects on laboratory tests

Rarely treatment with fluvoxamine has been associated with an increase in hepatic enzymes, mostly accompanied by clinical symptoms. In these cases, treatment should be discontinued.

Effects on other laboratory tests have not been established.

4.5 Interaction with other medicines and other forms of interaction

Pharmacodynamic interactions

Fluvoxamine is a serotonergic medicine and it can potentiate the effects of other serotonergic medicines. In rare cases this could lead to the development of a serotonergic syndrome of a serotonin syndrome or neuroleptic malignant syndrome (NMS)-like events. As these syndromes may result in potentially life-threatening conditions, treatment with fluvoxamine should be discontinued if such events (characterised by clusters of symptoms such as hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, mental status changes including confusion, hypomania, extreme agitation progressing to delirium and coma) occur and supportive symptomatic treatment should be initiated.

Fluvoxamine should not be used in combination with monoamine oxidase inhibitors (MAOI) including linezolid, due to risk of serotonin syndrome (see section 4.3). It should be used with caution in combination with other SSRIs, tricyclic antidepressants, tryptophan, triptans , phentermine, or tramadol.

Although fluvoxamine has been used in combination with lithium in the treatment of severely ill, drug-resistant patients, possible potentiation of serotonergic effect should be kept in mind.

As with other SSRIs, possible potentiation of an increased serotonergic effect should be considered where preparations containing St. John's Wort are used in combination with fluvoxamine.

As with other psychotropic agents, patients should be advised to avoid using alcohol while taking fluvoxamine.

When fluvoxamine was co-administered with warfarin for 2 weeks, plasma prothrombin times were prolonged. This can be ascribed to the intrinsic ability of SSRIs to lower the serotonin concentration in blood platelets (which can lead to prolonged bleeding in sensitive patients), and to fluvoxamine increasing the warfarin plasma concentrations. Patients receiving oral anticoagulants should have their prothrombin time monitored and their anticoagulant dose adjusted accordingly when administered fluvoxamine.

Medicines that prolong the QT interval

The risk of QTc prolongation and/or ventricular arrhythmias (eg. torsades de pointes) is increased with concomitant use of other medicines which prolong the QTc interval (eg. some antipsychotics and antibiotics). Please check the data sheet of other medicines administered for information on their effects on the QTc interval (see section 4.4).

Pharmacokinetic interactions

Fluvoxamine can inhibit the metabolism of drugs metabolised by certain P450 isoenzymes. A strong inhibition of CYP1A2 and CYP2C19 is demonstrated in *in vitro* and *in vivo* studies. CYP2C9, CYP2D6 and CYP3A4 are inhibited to a lesser extent. Fluvoxamine increases or decreases (e.g. in case of prodrugs like clopidogrel) the plasma concentrations of active substance/metabolites of drugs which are largely metabolised via these isoenzymes.

Concomitant therapy of fluvoxamine and these drugs should be initiated at or adjusted to the low end of their dosage range. Plasma concentrations, effects or adverse effects of co-administered drugs should be monitored and their dosage should be reduced if necessary. This is particularly relevant for drugs with a narrow therapeutic index.

CYP1A2

Tricyclic antidepressants and neuroleptics

An increase in previously stable plasma levels of those tricyclic antidepressants (such as clomipramine, amitriptyline and imipramine) and neuroleptics (or antipsychotics such as clozapine, olanzapine, quetiapine) which are largely metabolized through CYP1A2 has been reported when used together with fluvoxamine. The combination of fluvoxamine with these drugs is not recommended.

Compounds with a narrow therapeutic index

Patients co-administered fluvoxamine and CYP1A2 metabolised drugs with a narrow therapeutic index (such as tacrine, theophylline, methadone, mexiletine, phenytoin, carbamazepine and cyclosporine) should be carefully monitored when these agents are metabolized exclusively or by a combination of CYPs inhibited by fluvoxamine. If necessary, dose adjustment of these drugs is recommended.

When given with fluvoxamine, warfarin plasma concentration were significantly increased and prothrombin time prolonged.

Cases of increased side effects

Isolated cases of cardiac toxicity have been reported when fluvoxamine was combined with thioridazine.

Caffeine plasma levels are likely to be increased during co-administration with fluvoxamine. Thus, patients who consume high quantities of caffeine-containing beverages should lower their intake

when fluvoxamine is administered and adverse caffeine effects (like tremor, palpitations, nausea, restlessness, insomnia) are observed.

Terfenadine, astemizole, and cisapride (see section 4.4), sildenafil.

CYP3A4

When combined with fluvoxamine, plasma concentrations of cisapride may be increased resulting in an increased risk of QT-prolongation/Torsade de Pointes. Therefore fluvoxamine should not be co-administered with cisapride.

The plasma concentrations of benzodiazepines metabolised by oxidation (such as triazolam, midazolam, alprazolam and diazepam) are likely to increase when co-administered with fluvoxamine. The dosages of these benzodiazepines should be reduced during co-adminstration with fluvoxamine. For benzodiazepines metabolised by glucuronidation (lorazepam, lormetazepam, oxazepam, temazepam) or nitro-reduction (clonazepam, nitrazepam) such an effect is not likely to occur.

Increased serum concentrations of haloperidol have also been reported after concomitant use of haloperidol and fluvoxamine.

Patients co-administered fluvoxamine and CYP3A4 metabolised drugs with a narrow therapeutic index (e.g. cyclosporin, methadone or carbamazepine) should be carefully monitored and, if necessary, dose adjustments of these drugs is recommended.

CYP2C

Patients co-administered fluvoxamine and CYP2C metabolised drugs with a narrow therapeutic index (such as phenytoin) should be carefully monitored and, if necessary, dose adjustments of these drugs is recommended.

Cases of increased plasma concentration

As plasma concentrations of ropinirole may be increased in combination with fluvoxamine thus increasing the risk of overdose, surveillance and reduction in the dosing of ropinirole during fluvoxamine treatment and after its withdrawal may be required.

As plasma concentrations of propanolol are increased in combination with fluvoxamine, the propanolol dose may need to be lowered.

Other

No interactions were seen with digoxin or atenolol, which are renally excreted.

After a single oral dose, fluvoxamine plasma concentrations were lower in smokers than in non-smokers.

4.6 Fertility, pregnancy and lactation

Pregnancy

Category C.

Epidemiological data have suggested that the use of selective serotonin reuptake inhibitors (SSRIs) in pregnancy, particularly in late pregnancy, may increase the risk of persistent pulmonary hypertension in the newborn (PPHN). The observed risk was approximately 5 cases per 100 pregnancies. In the general population 1 to 2 cases of PPHN occur per 1000 pregnancies.

Fluvoxamine should not be used during pregnancy unless the clinical condition of the woman requires such treatment.

Isolated cases of withdrawal symptoms in the newborn child have been described after the use of fluvoxamine at the end of pregnancy. Neonates exposed to Luvox, other SNRIs (Serotonin and Norepinephrine Reuptake Inhibitors), or SSRIs (Selective Serotonin Reuptake Inhibitors), late in the third trimester have developed complications requiring prolonged hospitalization, respiratory support, and tube feeding. Such complications can arise immediately upon delivery. Reported clinical findings have included respiratory distress, cyanosis, apnea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycaemia, hypotonia, hypertonia, hyperreflexia, tremor, jitteriness, lethargy, somnolence, difficulty in sleeping, irritability and constant crying. These features are consistent with either a direct effect of SSRIs and SNRIs or, possibly, a drug discontinuation syndrome.

Breast feeding

Fluvoxamine is excreted via human milk in small quantities. Therefore, the medicine should not be used by women who are breast feeding.

Fertility

No data available. For pre-clinical fertility data refer to section 5.3.

4.7 Effects on ability to drive and use machines

Fluvoxamine at doses up to 150 mg per day exhibited no effect on psychomotor skills associated with driving and operating machinery in healthy volunteers. However, somnolence has been reported during treatment with fluvoxamine. Therefore, caution is recommended until the individual response to the drug has been determined.

4.8 Undesirable effects

Nausea, sometimes accompanied by vomiting, is the most frequently observed symptom associated with fluvoxamine treatment. This side effect usually diminishes within the first two weeks of treatment. Other adverse events, observed in clinical studies at frequencies listed below (database size approx - 35,000 patients; dose range 50-300 mg/day), are often associated with the illness and are not necessarily related to treatment.

Events are listed within body systems and categorised by frequency according to the following definitions:

Frequency estimate:

Very common (>10%)
Common (≥ 1 and <10 %)
Uncommon (≥ 0.1% and < 1 %)
Rare (≥ 0.01% and < 0.1 %)
Very rare (< 0.01 %)
Not known (cannot be estimated from the available data)

Table 1. – Undesirable effects

MedDra system organ class	Common	Uncommon	Rare	Very rare	Frequency not known
Endocrine disorders					Hyperprolactinaemia, inappropriate antidiuretic hormone secretion
Metabolism and nutrition disorders	Anorexia				Hyponatraemia, weight increased, weight decreased
Psychiatric disorders		Hallucination, confusional	Mania		Suicidal ideation, Suicidal behaviour

		stage, aggression			
Nervous system disorders	Agitation, nervousness, anxiety, insomnia, somnolence, tremor, headache, dizziness	Extrapyramidal disorder, ataxia	Convulsion		Serotonin syndrome, neurpleptic malignant syndrome-like events, akathisia/psychomotor restlessness, paraesthesia, dysgeusia
Eye disorders					Glaucoma, mydriasis
Cardiac disorders	Palpitations/ tachycardia	QTc prolongation and Torsades de Pointes			
Vascular disorders		(Orthostatic) hypotension			Haemhorrhage (e.g. gastrointestinal haemorrhage, gynaecological haemorrhage, ecchymosis, purpura)
Gastrointestinal disorders	Abdominal pain, constipation, diarrhoea, dry mouth, dyspepsia, nausea, vomiting				
Hepatobiliary disorders			Hepatic function abnormal		
Skin and subcutaneous disorders	Hyperhydrosis	Cutaneous hypersensitivity reactions (including angioneurotic oedema, rash, pruritis)	Photosensitivity reaction		
Musculoskeletal, connective tissue and bone disorders		Arthralgia, myalgia			* Bone fractures
Renal and Urinary disorders					Micturition disorder (including urinary retention, urinary incontinence, pollakiuria, nocturia and enuresis)
Reproductive system and breast disorders		Abnormal (delayed) ejaculation	Galactorrhoea		Anorgasmia, menstrual disorders (such as amenorrhoea, hypomenorrhoea, metrorrhagia, menorrhagia
General disorders and administration site reactions	Asthenia, malaise				Drug withdrawal syndrome including drug withdrawal syndrome neonatal

* Epidemiological studies, mainly conducted in patients 50 years of age and older, show an increased risk of bone fractures in patients receiving SSRIs and TCAs. The mechanism leading to this risk is unknown.

Withdrawal symptoms seen on discontinuation of fluvoxamine treatment

Discontinuation of fluvoxamine treatment (particularly when abrupt) commonly leads to withdrawal symptoms. It is therefore advised that when fluvoxamine treatment is no longer required, gradual discontinuation by dose tapering should be carried out (see sections 4.2 and 4.4).

Post-marketing data

As with other SSRIs, hyponatraemia has been rarely reported with fluvoxamine and appeared to be reversible when fluvoxamine was discontinued. Some cases were probably due to the syndrome of inappropriate antidiuretic hormone secretion. The majority of reports were associated with older patients.

Haemorrhage ecchymoses, purpura and gastrointestinal bleeding have been reported (see section 4.4).

Changes in weight (weight gain or weight loss) have also been reported.

Very rarely, paresthesia, taste perversion, visual disturbance and hepatitis have been reported.

Urogenital: Very rare - anorgasmia and impotence.

Skin: Uncommon - cutaneous hypersensitivity reaction (including angioedema).

Other adverse events in OCD paediatric population

In paediatric patients (N=57) treated with fluvoxamine the overall profile of adverse events was generally similar to that seen in adult studies. However the following events not appearing above have been reported in two or more of the paediatric patients and were more frequent with fluvoxamine than placebo: abnormal thinking, cough increase, dysmenorrhoea, emotional lability, epistaxis, hyperkinesia, infection and sinusitis.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/reporting/

4.9 Overdose

Symptoms

The most common symptoms of overdose include gastrointestinal complaints (nausea, vomiting and diarrhoea). Somnolence and dizziness, cardiac events (tachycardia, bradycardia, hypotension, QTc prolongation, Torsade de Pointes), liver function disturbances, convulsions and coma have also been reported.

More than 300 cases of deliberate overdosage with fluvoxamine have been reported to date. The highest documented dose of fluvoxamine ingested by a patient is 12 gram. This patient recovered completely.

Occasionally, more serious complications have been observed in cases of deliberate overdosage of fluvoxamine in combination with other medicines. Two deaths due to an overdose of fluvoxamine alone have been reported.

Treatment

There is no specific antidote to fluvoxamine. Treatment should consist of general measures employed in the management of overdose along with general symptomatic and supportive measures.

For further advice on management of overdose please contact the National Poisons Information Centre (0800 POISON or 0800 764 766).

5. Pharmacological Properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antidepressants, Selective serotonin reuptake inhibitor.

ATC code: N06AB08

Fluvoxamine is a member of a class of antidepressant agents known as selective serotonin reuptake inhibitors (SSRI). It is chemically unrelated to the tricyclic antidepressants, and to other serotonin reuptake inhibitors as it is a monocyclic compound.

Fluvoxamine maleate is a white to slightly off-white, odourless, crystalline powder, sparingly soluble in water, freely soluble in ethanol and chloroform, practically insoluble in diethylether. It has a partition coefficient (n-octanol/water, own pH) P=38.7.

Mechanism of action

The mechanism of action of fluvoxamine is believed to be related to its ability to selectively inhibit presynaptic reuptake of serotonin, and thus increase the serotonin concentrations within the synaptic cleft. This is accompanied by minimal interference with the noradrenergic processes.

Pharmacodynamic effects

Fluvoxamine has two isomeric forms: an E isomer which is pharmacologically active, and a Z isomer which is non-active. Luvox tablets contain only the E isomer.

Unlike tricyclic antidepressants, fluvoxamine has limited affinity for alpha adrenergic, beta adrenergic, histaminergic, muscarinic, dopaminergic or serotoninergic receptors. Antagonism of these post-synaptic receptors is believed to be associated with some of the cardiovascular, anticholinergic and sedative effects of certain other tricyclic antidepressant agents.

Dose-dependent decreases in rapid eye movement (REM) sleep and increased REM latency were found with fluvoxamine. These effects are similar to those of other antidepressant drugs.

Clinical efficacy and safety

Depression

In depression, the efficacy of fluvoxamine was established in 15 three-way trials in which fluvoxamine (≥100mg/day) was compared with both placebo and a tricyclic antidepressant (imipramine ≥ 150mg/day or desipramine, ≥100mg/day) generally over a period of 6 weeks and using HAM-D, CGI severity and MADRS as the main efficacy criteria. Of these studies, seven showed conclusive results: four were positive for both fluvoxamine and active reference therapy, whereas the other three studies showed only efficacy for active reference therapy. In a pooled analysis of the results of all these studies, both fluvoxamine (n=837) and active reference therapy (n=779) were found to be more effective than placebo (n=837). HAM-D improvements (LOCF) after 6 weeks were 39.1%, 41.9% and 33.9%, respectively. In these studies, the effective dose range for fluvoxamine was determined to lie between 100mg and 300mg per day. Using various definitions of response based on HAM-D or CGI criteria, there were no statistically significant differences in response rates between fluvoxamine and active reference therapy. Statistical analyses of the data did not reveal any patient features (such as age, sex, race etc.) which predict treatment response to fluvoxamine.

Prevention of relapse of depression

A study of depressed outpatients who had responded to fluvoxamine (MADRS ≤ 10) during an initial 26 week open treatment phase (n=204) and were then double-blind randomised to continuation on fluvoxamine (100mg/day) or placebo for 1 year demonstrated a significantly lower relapse rate for fluvoxamine (13%) compared to those on placebo (35%).

Obsessive compulsive disorder

Adult OCD Studies

The effectiveness of fluvoxamine in the treatment of Obsessive Compulsive Disorder (OCD) was demonstrated in two 10-week placebo-controlled studies (Studies 1 and 2). The results of two 10 week clomipramine-controlled studies (Studies 3 and 4) support the effectiveness of fluvoxamine in the treatment of OCD.

Studies 1 and 2 were flexible dose double-blind parallel group, multicentre studies in which patients with moderate to severe OCD received fluvoxamine in doses up to 300mg/day or placebo. 157 patients received fluvoxamine versus 158 patients who received placebo. Improvements from baseline in Yale-Brown Obsessive Compulsive Disorder (Y-BOCS) and NIMH-OC scores and the CGI improvement score were significantly greater in fluvoxamine-treated patients. In these studies, the overall response rates were 36% for fluvoxamine and 12% for placebo, and the effective dosage range for fluvoxamine was between 100mg and 300mg daily. In open extension studies, efficacy in OCD was demonstrated to be maintained in a total of 72 patients treated for a total of 46 weeks or more.

Studies 3 and 4 were flexible dose double-blind parallel group multicentre studies comparing fluvoxamine (100-300mg/day) with clomipramine (100mg-250mg/day). 69 patients received fluvoxamine versus 76 patients who received clomipramine. Fluvoxamine and clomipramine were equally efficacious on the Y-BOCS, NIMH-OC and CGI improvement scores.

Paediatric OCD Study

The effectiveness of fluvoxamine for the treatment of OCD was also demonstrated in a 10-week multicentre, parallel group, placebo-controlled study in a paediatric outpatient population (children and adolescents, ages 8-17) followed by an open-label extension of up to two years.

In the double-blind phase of the study, patients were titrated to a total daily fluvoxamine dose of approximately 100mg/day over the first two weeks of the trial, following which the dose was adjusted within a range of 50-200mg/day (on a b.i.d. schedule) on the basis of response and tolerance. All patients had moderate to severe OCD (DSM-III-R) with mean baseline ratings on the Children's Yale-Brown Obsessive Compulsive Scale (CY-BOCS), total score of 24. Patients receiving fluvoxamine maleate experienced mean reductions of approximately 6 units on the CY-BOCS total score, compared to a 3 unit reduction for placebo patients.

The following table provides the outcome classification by treatment group on the Global Improvement item of the Clinical Global Impression (CGI) scale for the paediatric study.

OUTCOME CLASSIFICATION (%) ON CGI-GLOBAL IMPROVEMENT ITEM FOR COMPLETERS IN PAEDIATRIC STUDY		
Outcome Classification	**Fluvoxamine (N=38)**	**Placebo (N=36)**
Very Much Improved	21%	11%
Much Improved	18%	17%
Minimally Improved	37%	22%
No change	16%	44%
Worse	8%	6%

Post hoc exploratory analyses for gender effects on outcomes did not suggest any differential responsiveness on the basis of gender. Further exploratory analyses revealed a prominent treatment effect in the 8-11 age group and essentially no effect in the 12-17 age group. The reason for the difference in these results is unknown. However, follow up data from the open extension of the study showed a further improvement as demonstrated by a decrease of an additional 3 to 6 units on the CY-BOCS in young, as well as adolescent, patients. This improvement was sustained over a one-year period in 54 of the 98 patients who completed the one-year extension and in 12 of the 22 patients who completed the two year extension.

Absorption

Fluvoxamine is almost completely absorbed following oral administration. The absolute bioavailability is 53% (90% confidence interval: 44-62%). Absorption is unaffected by the presence of food.

Distribution

Maximum plasma levels occur within 3-8 hours of dosing. Steady state levels are usually achieved within one week. The mean plasma half-life is approximately 12-13 hours after a single dose and approximately 22 hours following repeated dosing.

In vitro binding of fluvoxamine to human plasma proteins is 80%, and the volume of distribution is estimated to be 20 L/kg.

Biotransformation

Fluvoxamine undergoes extensive hepatic transformation, mainly via oxidative demethylation, into at least 9 metabolites. The two principal metabolites exhibit negligible pharmacological activity. In view of the structures of the other metabolites, it is not expected that the other metabolites would be pharmacologically active.

Elimination

Less than 4% of the dose is excreted in the urine as unchanged parent compound, while approximately 94% of the dose is recovered in the urine as metabolites.

The pharmacokinetics of fluvoxamine in patients with renal dysfunction do not appear to differ significantly from those in healthy, young volunteers. The area under the plasma concentration-time curve (AUC) and half-life were greater, however, in patients with liver dysfunction.

Patients suffering from renal or hepatic insufficiency should be carefully monitored when treated with fluvoxamine. Upward dose titration should be carried out more slowly in this patient population.

Linearity/non-linearity

The pharmacokinetics of fluvoxamine is linear between single oral doses of 25-100 mg. During multiple dosing in the range of 100-300 mg per day, the higher doses produced disproportionally higher plasma concentrations than predicted from data obtained with the lower dose.

Paediatric population

The multiple-dose pharmacokinetics of fluvoxamine was determined in male and female children (ages 6-11) and adolescents (ages 12-17). The clearance of fluvoxamine in children was approximately half that observed in adolescents. AUC and C_{max} in children were 1.5 to 2.7 fold higher than that in adolescents. As in adults, both children and adolescents exhibited non-linear multi-dose pharmacokinetics. Female children showed significantly lower clearance values and higher AUC (0-12) and C_{max} compared to male children and, therefore, lower doses of Luvox may produce therapeutic benefit. No gender differences were observed in adolescents. Body weight adjusted

mean clearance at a dose of 300mg/day was approximately 50% higher in adolescents compared to adults in previous studies.

5.3 Preclinical safety data

Carcinogenicity, mutagenicity, impairment of fertility

In animal studies, there was no evidence of carcinogenic activity when fluvoxamine was given to rats at dietary doses up to 211mg/kg/day for 30 months (approximately 2-5 times the maximum human exposure, based on plasma AUC), or to hamsters at about the same dose level for 112 weeks (male) and 85 weeks (female) (approximately two thirds the maximum human exposure, based on plasma AUC). No evidence of mutagenicity or chromosomal damage was observed *in vitro*. An *in vivo* test for chromosomal damage in mice (micronucleus test) gave no clear evidence of clastogenic activity.

Reproduction studies in animals revealed impaired fertility (Note: at doses exceeding 2 times the maximum recommended human dosage), increased embryofoetal death, decreased foetal body weight and increased incidences of foetal eye abnormalities (folded retina) in fluvoxamine doses which markedly exceed maximum recommended human dose.

The potential risk for humans is unknown.

No evidence of impairment of fertility in male and female rats was observed with fluvoxamine at oral doses up to 80 mg/kg/day.

6. Pharmaceutical Particulars

6.1 List of excipients

In addition to the drug substance, Luvox film coated tablets also contain mannitol, maize starch, pre gelatinised potato starch, sodium stearylfumarate, colloidal anhydrous silica, hypromellose, macrogol 6000, talc, titanium dioxide.

Luvox is lactose-free and gluten-free.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Store at or below 25℃.

6.5 Nature and contents of container

Luvox 50mg: PVC/PVDC/Al blister packs. Pack-sizes of 10, 30 or 60 tablets.

Luvox 100mg: PVC/PVDC/Al blister packs. Pack-sizes of 10 or 30 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Not applicable.

7. Medicines Schedule

8. Sponsor Details

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9. Date of First Approval

11 June 1998

10. Date of Revision of the Text

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