Prizma Solution

20mg per 5ml oral solution

1. Name of the medicinal product

Prizma Solution 20mg per 5ml oral solution.

2. Qualitative and quantitative composition

Each 5 ml of oral solution contains 20 mg of fluoxetine (as fluoxetine hydrochloride). <u>Excipients with known effect</u>: contains 3 g of sucrose per 5 ml dose. For the full list of excipients, see section 6.1

3. Pharmaceutical form

The solution is clear, colourless to yellowish.

4. Clinical particulars

4.1 Therapeutic indications

Major Depressive Disorder

Prizma solution is indicated for the treatment of Major Depressive disorder, with or without associated anxiety symptoms, especially where sedation is not required.

The usefulness of the drug in patients receiving fluoxetine for extended periods should periodically be reevaluated.

Obsessive Compulsive Disorder

Prizma solution is indicated for the treatment of obsessions and compulsions in patients with Obsessive Compulsive Disorder (OCD).

The effectiveness of Prizma solution in long-term use, i.e., for more than 13 weeks, has not been systematically evaluated in placebo-controlled trials. Therefore, the physician who elects to use Prizma solution for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient.

Bulimia Nervosa

Prizma solution is indicated for the acute and maintenance treatment of binge-eating and vomiting behaviors in adult patients with moderate to severe Bulimia Nervosa.

The physician who elects to use Prizma solution for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient.

4.2 Posology and method of administration

Major Depressive Disorder

Initial Treatment

In controlled trials used to support the efficacy of fluoxetine, patients were administered morning doses ranging from 20 to 80 mg/day. Studies comparing fluoxetine 20, 40, and 60 mg/day to placebo indicate that 20 mg/day is sufficient to obtain a satisfactory response in Major Depressive Disorder in most cases. Consequently, a dose of 20 mg/day, administered in the morning, is recommended as the initial dose. A dose increase may be considered after several weeks if insufficient clinical improvement is observed. Doses above 20 mg/day may be administered on a once-a-day (morning) or BID schedule (i.e., morning and noon) and should not exceed a maximum dose of 80 mg/day.

All patients — As with other drugs effective in the treatment of Major Depressive Disorder, the full effect may be delayed until 4 weeks of treatment or longer.

Patients with depression should be treated for a sufficient period of at least 6 months to ensure that they are free from symptoms.

Maintenance/Continuation/Extended Treatment — It is generally agreed that acute episodes of Major Depressive Disorder require several months or longer of sustained pharmacologic therapy. Whether the dose needed to induce remission is identical to the dose needed to maintain and/or sustain euthymia is unknown.

Daily Dosing — Systematic evaluation of FLUOXETINE in adult patients has shown that its efficacy in Major Depressive Disorder is maintained for periods of up to 38 weeks following 12 weeks of open-label acute treatment (50 weeks total) at a dose of 20 mg/day.

Switching Patients to a Tricyclic Antidepressant (TCA) — Dosage of a TCA may need to be reduced, and plasma TCA concentrations may need to be monitored temporarily when fluoxetine is coadministered or has been recently discontinued.

Obsessive Compulsive Disorder

Initial Treatment

In the controlled clinical trials of fluoxetine supporting its effectiveness in the treatment of OCD, patients were administered fixed daily doses of 20, 40, or 60 mg of fluoxetine or placebo. In one of these studies, no dose-response relationship for effectiveness was demonstrated. Consequently, a dose of 20 mg/day, administered in the morning, is recommended as the initial dose. Since there was a suggestion of a possible dose-response relationship for effectiveness in the second study, a dose increase may be considered after several weeks if insufficient clinical improvement is observed. The full therapeutic effect may be delayed until 5 weeks of treatment or longer. If no improvement is observed within 10 weeks, treatment with fluoxetine should be reconsidered.

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

Maintenance/Continuation Treatment — While there are no systematic studies that answer the question of how long to continue FLUOXETINE, OCD is a chronic condition, and it is reasonable to consider continuation for a responding patient. Although the efficacy of FLUOXETINE after 13 weeks has not been documented in controlled trials, adult patients have been continued in therapy under double-blind conditions for up to an additional 6 months without loss of benefit. 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.

Bulimia Nervosa

Initial Treatment — In the controlled clinical trials of fluoxetine supporting its effectiveness in the treatment of Bulimia Nervosa, patients were administered fixed daily fluoxetine doses of 20 or 60 mg, or placebo. Only the 60 mg dose was statistically significantly superior to placebo in reducing the frequency of binge-eating and vomiting. Consequently, the recommended dose is 60 mg/day, administered in the morning. For some patients it may be advisable to titrate up to this target dose over several days. Fluoxetine doses above 60 mg/day have not been systematically studied in patients with bulimia. *Maintenance/Continuation Treatment* — Systematic evaluation of continuing FLUOXETINE 60 mg/day for periods of up to 52 weeks in patients with bulimia who have responded while taking FLUOXETINE 60 mg/day during an 8-week acute treatment phase has demonstrated a benefit of such maintenance treatment. Nevertheless, patients should be periodically reassessed to determine the need for maintenance treatment.

Elderly patients

Caution is recommended when increasing the dose and the daily dose should generally not exceed 40 mg. Maximum recommended dose is 60 mg/day.

Patients with hepatic impairment

A lower or less frequent dose (e.g. 20 mg every second day) should be considered in patients with hepatic impairment, or in patients where concomitant medication has the potential for interaction with Fluoxetine.

Dosing in Specific Populations

Treatment of Pregnant Women — When treating pregnant women with FLUOXETINE, the physician should carefully consider the potential risks and potential benefits of treatment. Neonates exposed to SSRI or SNRIs late in the third trimester have developed complications requiring prolonged hospitalization, respiratory support, and tube feeding.

Geriatric — A lower or less frequent dosage should be considered for the elderly.

Hepatic Impairment — As with many other medications, use a lower or less frequent dosage should be used in patients with hepatic impairment.

Concomitant Illness — Patients with concurrent disease or on multiple concomitant medications may require dosage adjustments.

Discontinuation of Treatment

Symptoms associated with discontinuation of fluoxetine, SNRIs, and SSRIs, have been reported. *Withdrawal symptoms seen on discontinuation of FLUOXETINE:* 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 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.

Switching a Patient To or From a Monoamine Oxidase Inhibitor (MAOI) Intended to Treat Psychiatric Disorders

At least 14 days should elapse between discontinuation of an MAOI intended to treat psychiatric disorders and initiation of therapy with FLUOXETINE. Conversely, at least 5 weeks should be allowed after stopping FLUOXETINE before starting an MAOI intended to treat psychiatric disorders.

Use of FLUOXETINE with Other MAOIs such as Linezolid or Methylene Blue

Do not start FLUOXETINE in a patient who is being treated with linezolid or intravenous methylene blue because there is an increased risk of serotonin syndrome. In a patient who requires more urgent treatment of a psychiatric condition, other interventions, including hospitalization, should be considered.

In some cases, a patient already receiving FLUOXETINE therapy may require urgent treatment with linezolid or intravenous methylene blue. If acceptable alternatives to linezolid or intravenous methylene blue treatment are not available and the potential benefits of linezolid or intravenous methylene blue treatment are judged to outweigh the risks of serotonin syndrome in a particular patient, FLUOXETINE should be stopped promptly, and linezolid or intravenous methylene blue can be administered. The patient should be monitored for symptoms of serotonin syndrome for five weeks or until 24 hours after the last dose of linezolid or intravenous methylene blue, whichever comes first. Therapy with FLUOXETINE may be resumed 24 hours after the last dose of linezolid or intravenous methylene blue.

The risk of administering methylene blue by non-intravenous routes (such as oral tablets or by local injection) or in intravenous doses much lower than 1 mg/kg with FLUOXETINE is unclear. The clinician should, nevertheless, be aware of the possibility of emergent symptoms of serotonin syndrome with such use.

Method of administration

For oral administration.

Fluoxetine may be administered as a single or divided dose, during or between meals. When dosing is stopped, active drug substances will persist in the body for weeks. This should be borne in mind when starting or stopping treatment.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1. Fluoxetine is contra-indicated in combination with irreversible, non-selective monoamine oxidase inhibitors (e.g. iproniazid) (see sections 4.4 and 4.5).

Fluoxetine is contra-indicated in combination with metoprolol used in cardiac failure (see section 4.5).

4.4 Special warnings and precautions for use

Suicide/suicidal thoughts or clinical worsening

Depression is associated with an increased risk of suicidal thoughts, self-harm and suicide (suiciderelated events). This risk persists until significant remission occurs. As improvement may not occur during the first few weeks or more of treatment, patients should be closely monitored until such improvement occurs. It is general clinical experience that the risk of suicide may increase in the early stages of recovery.

Other psychiatric conditions for which Prizma Solution is prescribed can also be associated with an increased risk of suicide-related events. In addition, these conditions may be co-morbid with major depressive disorder. The same precautions observed when treating patients with major depressive disorder should therefore be observed when treating patients with other psychiatric disorders. Patients with a history of suicide-related events, those exhibiting a significant degree of suicidal ideation prior to commencement of treatment are known to be at greater risk of suicidal thoughts or suicide attempts, and should receive careful monitoring during treatment. A meta-analysis of placebo-controlled clinical trials of antidepressants drugs in adult patients with psychiatric disorders showed an increased risk of suicidal behaviour with antidepressants compared to placebo in patients less than 25 years old. Close supervision of patients and in particular those at high risk should accompany drug therapy especially in early treatment and following dose changes. Patients (and caregivers of patients) should be alerted about the need to monitor for any clinical worsening, suicidal behaviour or thoughts and unusual changes in behaviour and to seek medical advice immediately if these symptoms present. Cardiovascular Effects

Cases of QT interval prolongation and ventricular arrhythmia including torsades de pointes have been reported during the post-marketing period (see sections 4.5, 4.8 and 4.9).

Fluoxetine should be used with caution in patients with conditions such as congenital long QT syndrome, a family history of QT prolongation or other clinical conditions that predispose to arrhythmias (e.g., hypokalemia, hypomagnesemia, bradycardia, acute myocardial infarction or uncompensated heart failure) or increased exposure to fluoxetine (e.g., hepatic impairment), or concomitant use with medicinal products known to induce QT prolongation and/or torsade de pointes (see section 4.5).

If patients with stable cardiac disease are treated, an ECG review should be considered before treatment is started.

If signs of cardiac arrhythmia occur during treatment with fluoxetine, the treatment should be withdrawn and an ECG should be performed.

Irreversible, non-selective monoamine oxidase inhibitors (e.g. iproniazid)

Some cases of serious and sometimes fatal reactions have been reported in patients receiving an SSRI in combination with an irreversible, non-selective monoamine oxidase inhibitor (MAOI).

These cases presented with features resembling serotonin syndrome (which may be confounded with (or diagnosed as) neuroleptic malignant syndrome). Cyproheptadine or dantrolene may benefit patients experiencing such reactions. Symptoms of a drug interaction with a MAOI include: hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, mental status changes that include confusion, irritability and extreme agitation progressing to delirium and coma.

Therefore, fluoxetine is contra-indicated in combination with an irreversible, non-selective MAOI (see section 4.3). Because of the two weeks-lasting effect of the latter, treatment of fluoxetine should only be started 2 weeks after discontinuation of an irreversible, non-selective MAOI. Similarly, at least 5 weeks should elapse after discontinuing fluoxetine treatment before starting an irreversible, non-selective MAOI. Serotonin syndrome or neuroleptic malignant syndrome-like events

On rare occasions development of a serotonin syndrome or neuroleptic malignant syndrome-like events have been reported in association with treatment of fluoxetine, particularly when given in combination with other serotonergic (among others L-tryptophan) and/or neuroleptic drugs (see section 4.5). As these

syndromes may result in potentially life-threatening conditions, treatment with fluoxetine should be discontinued if such events (characterized by clusters of symptoms such as hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, mental status changes including confusion, irritability, extreme agitation progressing to delirium and coma) occur and supportive symptomatic treatment should be initiated.

<u>Mania</u>

Antidepressants should be used with caution in patients with a history of mania/hypomania. As with all antidepressants, fluoxetine should be discontinued in any patient entering a manic phase. <u>Haemorrhage</u>

SSRIs/SNRIs may increase the risk of postpartum haemorrhage (see sections 4.6, 4.8).

There have been reports of cutaneous bleeding abnormalities such as ecchymosis and purpura with SSRI's. Ecchymosis has been reported as an infrequent event during treatment with fluoxetine. Other haemorrhagic manifestations (e.g., gynaecological haemorrhages, gastrointestinal bleedings and other cutaneous or mucous bleedings) have been reported rarely. Caution is advised in patients taking SSRI's, particularly in concomitant use with oral anticoagulants, drugs known to affect platelet function (e.g. atypical antipsychotics such as clozapine, phenothiazines, most TCA's, aspirin, NSAID's) or other drugs that may increase risk of bleeding as well as in patients with a history of bleeding disorders (see section 4.5).

Seizures

Seizures are a potential risk with antidepressant drugs. Therefore, as with other antidepressants, fluoxetine should be introduced cautiously in patients who have a history of seizures. Treatment should be discontinued in any patient who develops seizures or where there is an increase in seizure frequency. Fluoxetine should be avoided in patients with unstable seizure disorders/epilepsy and patients with controlled epilepsy should be carefully monitored (see section 4.5).

Electroconvulsive Therapy (ECT)

There have been rare reports of prolonged seizures in patients on fluoxetine receiving ECT treatment, therefore caution is advisable.

<u>Tamoxifen</u>

Fluoxetine, a potent inhibitor of CYP2D6, may lead to reduced concentrations of endoxifen, one of the most important active metabolites of tamoxifen. Therefore, fluoxetine should whenever possible be avoided during tamoxifen treatment (see section 4.5).

Akathisia/psychomotor restlessness

The use of fluoxetine has been associated with the development of akathisia, characterised by a subjectively unpleasant or distressing restlessness and need to move often accompanied by an inability to sit or stand still. 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. Diabetes

In patients with diabetes, treatment with an SSRI 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.

Hepatic/Renal Function

Fluoxetine is extensively metabolized by the liver and excreted by the kidneys. A lower dose, e.g., alternate day dosing, is recommended in patients with significant hepatic dysfunction. When given fluoxetine 20 mg/day for 2 months, patients with severe renal failure (GFR <10 ml/min) requiring dialysis showed no difference in plasma levels of fluoxetine or norfluoxetine compared to controls with normal renal function.

Rash and allergic reactions

Rash, anaphylactoid events and progressive systemic events, sometimes serious (involving skin, kidney, liver or lung) have been reported. Upon the appearance of rash or of other allergic phenomena for which an alternative aetiology cannot be identified, fluoxetine should be discontinued.

Weight loss

Weight loss may occur in patients taking fluoxetine, but it is usually proportional to baseline body weight. Withdrawal symptoms seen on discontinuation of SSRI treatment Withdrawal symptoms when treatment is discontinued are common, particularly if discontinuation is abrupt (see section 4.8). In clinical trials, adverse events seen on treatment discontinuation occurred in approximately 60% of patients in both the fluoxetine and placebo groups. Of these adverse events, 17% in the fluoxetine group and 12% in the placebo group were severe in nature.

The risk of withdrawal symptoms may be dependent on several factors, including the duration and dose of therapy and the rate of dose reduction. 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. Generally, these symptoms are mild to moderate; however, in some patients they may be severe in intensity. They usually occur within the first few days of discontinuing treatment. Generally, these symptoms are self-limiting and usually resolve within 2 weeks, though in some individuals they may be prolonged (2-3 months or more). It is therefore advised that Prizma Solution should be gradually tapered when discontinuing treatment over a period of at least one to two weeks, according to the patient's needs (see *Withdrawal symptoms seen on discontinuation of* Prizma Solution, section 4.2).

<u>Mydriasis</u>

Mydriasis has been reported in association with fluoxetine; therefore, caution should be used when prescribing fluoxetine in patients with raised intraocular pressure or those at risk of acute narrow-angle glaucoma.

Sexual Dysfunction:

Selective serotonin reuptake inhibitors (SSRIs)/serotonin norepinephrine reuptake inhibitors (SNRIs) may cause symptoms of sexual dysfunction (see section 4.8). There have been reports of long-lasting sexual dysfunction where the symptoms have continued despite discontinuation of SSRIs/SNRI.

Prizma Solution oral solution contains sucrose

Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Half-life: The long elimination half-lives of both fluoxetine and norfluoxetine should be borne in mind (see section 5.2) when considering pharmacodynamic or pharmacokinetic drug interactions (e.g., when switching from fluoxetine to other antidepressants).

Contra-indicated combinations

Irreversible, non-selective monoamine oxidase inhibitors (e.g. iproniazid): Some cases of serious and sometimes fatal reactions have been reported in patients receiving an SSRI in combination with an irreversible, non-selective monoamine oxidase inhibitor (MAOI).

These cases presented with features resembling serotonin syndrome (which may be confounded with [or diagnosed as] neuroleptic malignant syndrome). Cyproheptadine or dantrolene may benefit patients experiencing such reactions. Symptoms of a drug interaction with a MAOI include: hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, mental status changes that include confusion, irritability and extreme agitation progressing to delirium and coma.

Therefore, fluoxetine is contra-indicated in combination with an irreversible, non-selective MAOI (see section 4.3). Because of the two weeks-lasting effect of the latter, treatment of fluoxetine should only be started 2 weeks after discontinuation of an irreversible, non-selective MAOI. Similarly, at least 5 weeks should elapse after discontinuing fluoxetine treatment before starting an irreversible, non-selective MAOI. *Metoprolol used in cardiac failure*: risk of metoprolol adverse events, including excessive bradycardia, may be increased because of an inhibition of its metabolism by fluoxetine (see section 4.3). *Not recommended combinations*

Tamoxifen: Pharmacokinetic interaction between CYP2D6 inhibitors and tamoxifen, showing a 65-75 % reduction in plasma levels of one of the more active forms of the tamoxifen, i.e. endoxifen, has been reported in the literature. Reduced efficacy of tamoxifen has been reported with concomitant usage of some SSRI antidepressants in some studies. As a reduced effect of tamoxifen cannot be excluded, co-administration with potent CYP2D6 inhibitors (including fluoxetine) should whenever possible be avoided (see section 4.4).

Alcohol: In formal testing, fluoxetine did not raise blood alcohol levels or enhance the effects of alcohol. However, the combination of SSRI treatment and alcohol is not advisable.

MAOI-A including linezolid and methylthioninium chloride (methylene blue): Risk of serotonin syndrome including diarrhoea, tachycardia, sweating, tremor, confusion or coma. If the concomitant use of these active substances with fluoxetine cannot be avoided, close clinical monitoring should be undertaken and the concomitant agents should be initiated at the lower recommended doses (see section 4.4). *Mequitazine*: risk of mequitazine adverse events (such as QT prolongation) may be increased because of an inhibition of its metabolism by fluoxetine.

Combinations requiring caution

Phenytoin: Changes in blood levels have been observed when combined with fluoxetine. In some cases manifestations of toxicity have occurred. Consideration should be given to using conservative titration schedules of the concomitant drug and to monitoring clinical status.

Serotoninergic drugs (lithium, tramadol, triptans, tryptophan, selegiline (MAOI-B), St. John's Wort (Hypericum perforatum)): There have been reports of mild serotonin syndrome when SSRIs were given with drugs also having a serotoninergic effect. Therefore, the concomitant use of fluoxetine with these drugs should be undertaken with caution, with closer and more frequent clinical monitoring (see section 4.4). Use with triptans carries the additional risk of coronary vasoconstriction and hypertension.

QT interval prolongation: Pharmacokinetic and pharmacodynamic studies between fluoxetine and other medicinal products that prolong the QT interval have not been performed. An additive effect of fluoxetine and these medicinal products cannot be excluded. Therefore, co-administration of fluoxetine with medicinal products that prolong the QT interval, such as Class IA and III antiarrhythmics, antipsychotics (e.g. phenothiazine derivatives, pimozide, haloperidol), tricyclic antidepressants, certain antimicrobial agents (e.g. sparfloxacin, moxifloxacin, erythromycin IV (intravenous), pentamidine), anti-malaria treatment particularly halofantrine, certain antihistamines (astemizole, mizolastine), should be used with caution (see sections 4.4, 4.8 and 4.9).

Drugs affecting haemostasis (oral anticoagulants, whatever their mechanism, platelets antiaggregants including aspirin and NSAIDs): Risk of increased bleeding. Clinical monitoring, and more frequent monitoring of INR with oral anticoagulants, should be made. A dose adjustment during the fluoxetine treatment and after its discontinuation may be suitable (see sections 4.4 and 4.8).

Cyproheptadine: There are individual case reports of reduced antidepressant activity of fluoxetine when used in combination with cyproheptadine.

Drugs inducing hyponatremia: Hyponatremia is an undesirable effect of fluoxetine. Use in combination with other agents associated with hyponatremia (e.g. diuretics, desmopressin, carbamazepine and oxcarbazepine) may lead to an increased risk (see section 4.8).

Drugs lowering the epileptogenic threshold: Seizures are an undesirable effect of fluoxetine. Use in combination with other agents which may lower the seizure threshold (for example, TCAs, other SSRIs, phenothiazines, butyrophenones, mefloquine, chloroquine, bupropion, tramadol) may lead to an increased risk.

Other drugs metabolised by CYP2D6: Fluoxetine is a strong inhibitor of CYP2D6 enzyme, therefore concomitant therapy with drugs also metabolised by this enzyme system may lead to drug interactions, notably those having a narrow therapeutic index (such as flecainide, encainide, propafenone and nebivolol) and those that are titrated, but also with atomoxetine, carbamazepine, tricyclic antidepressants and risperidone. They should be initiated at or adjusted to the low end of their dose range. This may also apply if fluoxetine has been taken in the previous 5 weeks.

4.6 Fertility, pregnancy and lactation

Pregnancy

Some epidemiological studies suggest an increased risk of cardiovascular defects associated with the use of fluoxetine during the first trimester. The mechanism is unknown. Overall the data suggest that the risk of having an infant with a cardiovascular defect following maternal fluoxetine exposure is in the region of 2/100 compared with an expected rate for such defects of approximately 1/100 in the general population.

Epidemiological data have suggested that the use of 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 1000 pregnancies. In the general population 1 to 2 cases of PPHN per 1000 pregnancies occur.

Fluoxetine should not be used during pregnancy unless the clinical condition of the woman requires treatment with fluoxetine and justifies the potential risk to the foetus. Abrupt discontinuation of therapy should be avoided during pregnancy (see section 4.2 "Posology and method of administration"). If fluoxetine is used during pregnancy, caution should be exercised, especially during late pregnancy or just prior to the onset of labour since some other effects have been reported in neonates: irritability, tremor, hypotonia, persistent crying, difficulty in sucking or in sleeping. These symptoms may indicate either serotonergic effects or a withdrawal syndrome. The time to occur and the duration of these symptoms may be related to the long half-life of fluoxetine (4-6 days) and its active metabolite, norfluoxetine (4-16 days).

Observational data indicate an increased risk (less than 2-fold) of potpartum haemorrhage following SSRI/SNRI exposure within the month prior to birth (see sections 4.4, 4.8).

Lactation

Fluoxetine and its metabolite norfluoxetine, are known to be excreted in human breast milk. Adverse events have been reported in breastfeeding infants. If treatment with fluoxetine is considered necessary, discontinuation of breastfeeding should be considered; however, if breastfeeding is continued, the lowest effective dose of fluoxetine should be prescribed.

Fertility

Animal data have shown that fluoxetine may affect sperm quality (see section 5.3).

Human case reports with some SSRI's 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

Prizma Solution has no or negligible influence on the ability to drive and use machines. Although fluoxetine has been shown not to affect psychomotor performance in healthy volunteers, any psychoactive drug may impair judgement or 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.

4.8 Undesirable effects

a. Summary of the safety profile

The most commonly reported adverse reactions in patients treated with fluoxetine were headache, nausea, insomnia, fatigue and diarrhoea. Undesirable effects may decrease in intensity and frequency with continued treatment and do not generally lead to cessation of therapy.

b. Tabulated list of adverse reactions

The table below gives the adverse reactions observed with fluoxetine treatment in adult and paediatric populations. Some of these adverse reactions are in common with other SSRIs.

The following frequencies have been calculated from clinical trials in adults (n = 9297) and from spontaneous reporting.

Frequency estimate: Very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000).

Very Common	Common	Uncommon	Rare	Not Known
Blood and lympha				
			Thrombocytopenia Neutropenia Leucopenia	
Immune system c				
			Anaphylactic reaction Serum sickness	
Endocrine disorde	ers			
			Inappropriate antidiuretic hormone secretion	

Metabolism and	d nutrition disorders			
	Decreased appetite ¹		Hyponatraemia	
Psychiatric disc	orders	·		
Insomnia ²	Anxiety Nervousness Restlessness Tension Libido decreased ³ Sleep disorder Abnormal dreams ⁴	Depersonalisation Elevated mood Euphoric mood Thinking abnormal Orgasm abnormal ⁵ Bruxism Suicidal thoughts and behaviour ⁶	Hypomania Mania Hallucinations Agitation Panic attacks Confusion Dysphemia Aggression	
Nervous syster	m disorders	1		
Headache	Disturbance in attention Dizziness Dysgeusia Lethargy Somnolence ⁷ Tremor	Psychomotor hyperactivity Dyskinesia Ataxia Balance disorder Myoclonus Memory impairment	Convulsion Akathisia Buccoglossal syndrome Serotonin syndrome	Hypoesthesia
Eye disorders				
	Vision blurred	Mydriasis		
Ear and labyrin	th disorders	1 -	1	
		Tinnitus		
Cardiac disorde	ers	1	1	
	Palpitations Electrocardiogram QT prolonged (QTcF ≥450 msec) ⁸		Ventricular arrhythmia including torsades de pointes	
Vascular disord	,	1	1	
	Flushing ⁹	Hypotension	Vasculitis Vasodilatation	
Respiratory, the	oracic and mediastinal dis	sorders		
	Yawning	Dyspnoea Epistaxis Dysphonia	Pharyngitis Pulmonary events (inflammatory processes of varying histopathology and/or fibrosis) ¹⁰	
Gastrointestina	l disorders			
Diarrhoea Nausea	Vomiting Dyspepsia Dry mouth	Dysphagia Gastrointestinal haemorrhage ¹¹	Oesophageal pain	
Hepato-biliary o	disorders			
			Idiosyncratic hepatitis	
Skin and subcu	Itaneous tissue disorders			<u>.</u>
	Rash ¹² Urticaria	Alopecia	Angioedema Ecchymosis	Erythromelalgia

	Pruritus Hyperhidrosis	Increased tendency to bruise Cold sweat	Photosensitivity reaction Purpura Erythema multiforme Stevens-Johnson syndrome Toxic Epidermal Necrolysis (Lyell Syndrome)	
Musculoskeletal a	and connective tissue o	lisorders	1	
	Arthralgia	Muscle twitching	Myalgia	
Renal and urinary	/ disorders			
	Frequent urination ¹³	Dysuria	Urinary retention Micturition disorder	
Reproductive sys	tem and breast disorde	ers		
	Gynaecological bleeding ¹⁴ Erectile dysfunction Ejaculation disorder ¹⁵	Sexual dysfunction	Galactorrhoea Hyperprolactinaemia Priapism	Postpartum haemorrhage ¹⁶
General disorders	s and administration sit	e conditions	1	
Fatigue ¹⁷	Feeling jittery Chills	Malaise Feeling abnormal Feeling cold Feeling hot	Mucosal haemorrhage	
Investigations				
	Weight decreased	Transaminases increased Gamma- glutamyltransferase increased Abnormal liver function tests		

¹ Includes anorexia

² Includes early morning awakening, initial insomnia, middle insomnia

³ Includes loss of libido

⁴ Includes nightmares

⁵ Includes anorgasmia

⁶ Includes completed suicide, depression suicidal, intentional self-injury, self-injurious ideation, suicidal behaviour, suicidal ideation, suicide attempt, morbid thoughts, self-injurious behaviour. These symptoms may be due to underlying disease

⁷ Includes hypersomnia, sedation

⁸ Based on ECG measurements from clinical trials

⁹ Includes hot flush

¹⁰ Includes atelectasis, interstitial lung disease, pneumonitis

¹¹ Includes most frequently gingival bleeding, haematemesis, haematochezia, rectal haemorrhage,

diarrhoea haemorrhagic, melaena, and gastric ulcerhaemorrhage

¹² Includes erythema, exfoliative rash, heat rash, rash, rash erythematous, rash follicular, rash

generalized, rash macular, rash macular-papular, rash morbilliform, rash papular, rash pruritic, rash vesicular, umbilical erythema rash

¹³ Includes pollakiuria

¹⁴ Includes cervix haemorrhage, uterine dysfunction, uterine bleeding, genital haemorrhage, menometrorhagia, menorrhagia, metrorrhagia, polymenorrhea, postmenopausal haemorrhage, uterine haemorrhage, vaginal haemorrhage

¹⁵ Includes ejaculation failure, ejaculation dysfunction, premature ejaculation, ejaculation delayed, retrograde ejaculation

¹⁶ This event has been reported for the therapeutic class of SSRIs/SNRIs (see sections 4.4, 4.6).
¹⁷ Includes asthenia

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

Withdrawal symptoms seen on discontinuation of fluoxetine treatments: Discontinuation of fluoxetine 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. Generally these events are mild to moderate and are self-limiting, however, in some patients they may be severe and/or prolonged (see section 4.4). It is therefore advised that when Prizma Solution treatment is no longer required, gradual discontinuation by dose tapering should be carried out (see sections 4.2 and 4.4).

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. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form. https://sideeffects.health.gov.il

4.9 Overdose

Symptoms

Cases of overdose of fluoxetine alone usually have a mild course. Symptoms of overdose have included nausea, vomiting, seizures, cardiovascular dysfunction ranging from asymptomatic arrhythmias (including nodal rhythm and ventricular arrhythmias) or ECG changes indicative of QTc prolongation to cardiac arrest (including very rare cases of Torsades de Pointes), pulmonary dysfunction, and signs of altered CNS status ranging from excitation to coma. Fatality attributed to overdose of fluoxetine alone has been extremely rare.

Rarely features of the "serotonin syndrome" may occur. This includes alteration of mental status' neuromuscular hyperactivity and autonomic instability. There may be hyperpyrexia and elevation of serum creatine kinase. Rhabdomyolysis is rare.

Management

Cardiac and vital signs monitoring are recommended, along with general symptomatic and supportive measures. No specific antidote is known.

Forced diuresis, dialysis, haemoperfusion, and exchange transfusion are unlikely to be of benefit. Activated charcoal, which may be used with sorbitol, may be as or more effective than emesis or lavage. In managing overdosage, consider the possibility of multiple drug involvement. An extended time for close medical observation may be needed in patients who have taken excessive quantities of a tricyclic antidepressant if they are also taking, or have recently taken, fluoxetine.

5. Pharmacological properties 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Selective serotonin reuptake inhibitors. *ATC code:* N06A B03. <u>Mechanism of action</u>

Fluoxetine is a selective inhibitor of serotonin reuptake, and this probably accounts for the mechanism of action. Fluoxetine has practically no affinity to other receptors such as α_1 -, α_2 -, and β -adrenergic; serotonergic; dopaminergic; histaminergic; muscarinic; and GABA receptors.

Clinical efficacy and safety

Major depressive episodes: Clinical trials in patients with major depressive episodes have been conducted versus placebo and active controls. Fluoxetine has been shown to be significantly more effective than placebo, as measured by the Hamilton Depression Rating Scale (HAM-D). In these studies, Fluoxetine produced a significantly higher rate of response (defined by a 50% decrease in the HAM-D score) and remission compared to placebo.

Dose response: In the fixed-dose studies of patients with major depression there is a flat dose response curve, providing no suggestion of advantage in terms of efficacy for using higher than the recommended doses. However, it is clinical experience that uptitrating might be beneficial for some patients. *Obsessive-compulsive disorder:* In short-term trials (under 24 weeks), fluoxetine was shown to be

significantly more effective than placebo. There was a therapeutic effect at 20mg/day, but higher doses (40 or 60mg/day) showed a higher response rate. In long-term studies (three short-term studies extension phase and a relapse prevention study), efficacy has not been shown.

Bulimia nervosa: In short-term trials (under 16 weeks), in out-patients fulfilling DSM-III-R-criteria for bulimia nervosa, fluoxetine 60mg/day was shown to be significantly more effective than placebo for the reduction of bingeing, vomiting and purging activities. However, for long-term efficacy no conclusion can be drawn.

Pre-Menstrual Dysphoric Disorder. Two placebo-controlled studies were conducted in patients meeting Pre-Menstrual Dysphoric Disorder (PMDD) diagnostic criteria according to DSM-IV. Patients were included if they had symptoms of sufficient severity to impair social and occupational function and relationships with others. Patients using oral contraceptives were excluded. In the first study of continuous 20mg daily dosing for 6 cycles, improvement was observed in the primary efficacy parameter (irritability, anxiety and dysphoria). In the second study, with intermittent luteal phase dosing (20mg daily for 14 days) for 3 cycles, improvement was observed in the primary efficacy parameter (Daily Record of Severity of Problems score). However, definitive conclusions on efficacy and duration of treatment cannot be drawn from these studies.

5.2 Pharmacokinetic properties

Absorption

Fluoxetine is well absorbed from the gastro-intestinal tract after oral administration. The bioavailability is not affected by food intake.

Distribution

Fluoxetine is extensively bound to plasma proteins (about 95%) and it is widely distributed (volume of distribution: 20-40 L/kg). Steady-state plasma concentrations are achieved after dosing for several weeks. Steady-state concentrations after prolonged dosing are similar to concentrations seen at 4 to 5 weeks. <u>Biotransformation</u>

Fluoxetine has a non-linear pharmacokinetic profile with first-pass liver effect. Maximum plasma concentration is generally achieved 6 to 8 hours after administration. Fluoxetine is extensively metabolised by the polymorphic enzyme CYP2D6. Fluoxetine is primarily metabolised by the liver to the active metabolite norfluoxetine (desmethylfluoxetine), by desmethylation. Elimination

The elimination half-life of fluoxetine is 4 to 6 days and for norfluoxetine 4 to 16 days. These long halflives are responsible for persistence of the drug for 5-6 weeks after discontinuation. Excretion is mainly (about 60%) via the kidney. Fluoxetine is secreted into breast milk.

Special populations

<u>Elderly</u>: Kinetic parameters are not altered in healthy elderly when compared to younger subjects. <u>Hepatic insufficiency</u>: In case of hepatic insufficiency (alcoholic cirrhosis), fluoxetine and norfluoxetine half-lives are increased to 7 and 12 days, respectively. A lower or less frequent dose should be considered.

<u>Renal insufficiency</u>: After single-dose administration of fluoxetine in patients with mild, moderate, or complete (anuria) renal insufficiency, kinetic parameters have not been altered when compared to healthy volunteers. However, after repeated administration, an increase in steady-state plateau of plasma concentrations may be observed.

5.3 Preclinical safety data

There is no evidence of carcinogenicity or mutagenicity from *in vitro* or animal studies.

Adult animal studies

In a 2-generation rat reproduction study, fluoxetine did not produce adverse effects on the mating or fertility of rats, was not teratogenic, and did not affect growth, development, or reproductive parameters of the offspring.

The concentrations in the diet provided doses approximately equivalent to 1.5, 3.9, and 9.7 mg fluoxetine/kg body weight.

Male mice treated daily for 3 months with fluoxetine in the diet at a dose approximately equivalent to 31 mg/kg showed a decrease in testis weight and hypospermatogenesis. However, this dose level exceeded the maximum-tolerated dose (MTD) as significant signs of toxicity were seen. *Juvenile animal studies*

In a juvenile toxicology study in CD rats, administration of 30 mg/kg/day of fluoxetine hydrochloride on postnatal days 21 to 90 resulted in irreversible testicular degeneration and necrosis, epididymal epithelial vacuolation, immaturity and inactivity of the female reproductive tract and decreased fertility. Delays in sexual maturation occurred in males (10 and 30 mg/kg/day) and females (30 mg/kg/day). The significance of these findings in humans is unknown. Rats administered 30 mg/kg also had decreased femur lengths compared with controls and skeletal muscle degeneration, necrosis and regeneration. At 10 mg/kg/day, plasma levels achieved in animals were approximately 0.8 to 8.8 fold (fluoxetine) and 3.6 to 23.2 fold (norfluoxetine) those usually observed in paediatric patients. At 3 mg/kg/day, plasma levels achieved in animals were approximately 0.3 to 2.1 fold (norfluoxetine) those usually achieved in paediatric patients.

A study in juvenile mice has indicated that inhibition of the serotonin transporter prevents the accrual of bone formation. This finding would appear to be supported by clinical findings. The reversibility of this effect has not been established.

Another study in juvenile mice (treated on postnatal days 4 to 21) has demonstrated that inhibition of the serotonin transporter had long-lasting effects on the behaviour of the mice. There is no information on whether the effect was reversible. The clinical relevance of this finding has not been established.

Adult animal studies

In a 2-generation rat reproduction study' fluoxetine did not produce adverse effects on the mating or fertility of rat, was not teratogenic, and did not affect growth, development, or reproductive parameters of the offspring.

The concentrations in the diet provided doses approximately equivalent to 1.5, 3.9, and 9.7 mg fluoxetine/kg body weight.

6. Pharmaceutical particulars 6.1 List of excipients

The oral solution contains: Sucrose Glycerol Benzoic acid Purified water

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.

6.4 Special precautions for storage

Oral solution: Store at a temperature below 25°C, and in a place protected from light

6.5 Nature and contents of container

120 ml Amber glass bottle

6.6 Special precautions for disposal and other handling

No special requirements. Manufacturer: Unipharm Ltd., "Mevo Carmel" Industrial Park License Holder: Unipharm Itd, 1 Shevet Shimon St. P.O. Box 21429, 6121301, Tel Aviv, Israel

7. Marketing authorisation holder

Unipharm Itd, 1 Shevet Shimon St. P.O. Box 21429, 6121301, Tel Aviv, Israel

8. Marketing authorisation number(s) 162 93 35206 01

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