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).
Excipients with known effect (also see section 4.4):
Prizma Solution 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, colorless to yellowish.

WARNING: SUICIDAL THOUGHTS AND BEHAVIORS
SUICIDALITY AND ANTI-DEPRESSANT DRUGS

Antidepressants increased the risk of suicidal thoughts and behavior in children, adolescents, and young adults in short-term trials. These trials did not show an increase in the risk of suicidal thoughts and behavior with antidepressant use in subjects aged 65 and older [see Special warnings and precautions for use (4.4)].

In patients of all ages who are started on antidepressant therapy, monitor closely for worsening, and for emergence of suicidal thoughts and behaviors. Advise families and caregivers of the need for close observation and communication with the prescriber [see Special warnings and precautions for use (4.4)].

4. Clinical particulars

4.1 Therapeutic indications

Adults:
Major depressive episodes.
Obsessive-compulsive disorder (OCD).
Bulimia nervosa: Fluoxetine is indicated as a complement of psychotherapy for the reduction of binge-eating and purging activity.

Children and adolescents aged 8 years and above:
Moderate to severe major depressive episode, if depression is unresponsive to psychological therapy after 4–6 sessions. Antidepressant medication should be offered to a child or young person with moderate to severe depression only in combination with a concurrent psychological therapy.

4.2 Posology and method of administration

Adults:

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 co-administered 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.

Pediatric population
Children and adolescents aged 8 years and above (Moderate to severe

major depressive episode)
Treatment should be initiated and monitored under specialist supervision. The starting dose is 10 mg/day fluoxetine (as hydrochloride) given as oral solution (there is a drug from another company, which comes as a solution). Dose adjustments should be made carefully, on an individual basis, to maintain the patient at the lowest effective dose.
After one to two weeks, the dose may be increased to 20 mg/day. Clinical trial experience with daily doses greater than 20 mg is minimal. There is only limited data on treatment beyond 9 weeks.

Lower weight children
Due to higher plasma levels in lower weight children, the therapeutic effect may be achieved with lower doses (see section 5.2).
For pediatric patients who respond to treatment, the need for continued treatment after 6 months should be reviewed. If no clinical benefit is achieved within 9 weeks, treatment should be reconsidered.

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

Pediatric population-Children and adolescents under 18 years of age:
Suicide-related behaviors (suicide attempt and suicidal thoughts) and hostility (predominantly aggression, oppositional behavior and anger) were more frequently observed in clinical trials among children and adolescents treated with antidepressants compared to those treated with placebo. Fluoxetine should only be used in children and adolescents aged 8 to 18 years for the treatment of moderate to severe major depressive episodes and it should not be used in other indications. If, based on clinical need, a decision to treat is nevertheless taken, the patient should be carefully monitored for the appearance of suicidal symptoms. In addition, only limited evidence is available concerning long-term effect on safety in children and adolescents, including effects on growth, sexual maturation and cognitive, emotional and behavioral developments (see section 5.3).

In a 19-week clinical trial, decreased height and weight gain was observed in children and adolescents treated with fluoxetine (see section 4.8). It has not been established whether there is an effect on achieving normal adult height. The possibility of a delay in puberty cannot be ruled out (see sections 5.3 and 4.8). Growth and pubertal development (height, weight and TANNER staging) should therefore be monitored during and after treatment with fluoxetine.
If either is slowed, referral to a pediatrician should be considered.

In pediatric trials, mania and hypomania were commonly reported (see section 4.8).
Therefore, regular monitoring for the occurrence of mania/hypomania is recommended.
Fluoxetine should be discontinued in any patient entering a manic phase.

It is important that the prescriber carefully discusses the risks and benefits of treatment with the child/young person and/or their parents.

Suicide/suicidal thoughts or clinical worsening
Depression is associated with an increased risk of suicidal thoughts, self-harm and suicide (suicide-related 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 behavior 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 behavior or thoughts and unusual changes in behavior 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 includes: 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.
Mania
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.
Hemorrhage.

SSRIs/SNRIs may increase the risk of postpartum hemorrhage (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 hemorrhagic manifestations (e.g., gynecological hemorrhages, 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.

Tamoxifen

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, characterized 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 glycemic control. Hypoglycemia has occurred during therapy with fluoxetine and hyperglycemia has developed following discontinuation. Insulin and/or oral hypoglycemic 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).

Mydriasis

Mydriasis has been reported in association with fluoxetine; therefore, caution should be used when prescribing fluoxetine in patients with raised intraocular pressure or those at risk of acute narrow-angle glaucoma.
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 diarrhea, 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 metabolized by CYP2D6: Fluoxetine is a strong inhibitor of CYP2D6 enzyme, therefore concomitant therapy with drugs also metabolized 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.

Pediatric population
Interaction studies have only been performed in adults.

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 fetus. 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 labor 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 postpartum hemorrhage 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 diarrhea. 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 pediatric 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 lymphatic system disorders				
			Thrombocytopenia Neutropenia Leucopenia	
Immune system disorders				
			Anaphylactic reaction Serum sickness	
Endocrine disorders				
			Inappropriate antidiuretic hormone secretion	
Metabolism and nutrition disorders				
	Decreased appetite[1]		Hyponatraemia	
Psychiatric disorders				
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 behavior [6]	Hypomania Mania Hallucinations Agitation Panic attacks Confusion Dysphemia Aggression	
Nervous system disorders				
Headache	Disturbance in attention Dizziness Dysgeusia Lethargy	Psychomotor hyperactivity Dyskinesia Ataxia Balance disorder	Convulsion Akathisia Buccoglossal syndrome Serotonin syndrome	Hypoesthesia

	Somnolence[7] Tremor	Myoclonus Memory impairment		
Eye disorders				
	Vision blurred	Mydriasis		
Ear and labyrinth disorders				
		Tinnitus		
Cardiac disorders				
	Palpitations Electrocardiogram QT prolonged (QTcF ≥450 msec)[8]		Ventricular arrhythmia including torsades de pointes	
Vascular disorders				
	Flushing[9]	Hypotension	Vasculitis Vasodilatation	
Respiratory, thoracic and mediastinal disorders				
	Yawning	Dyspnoea Epistaxis Dysphonia	Pharyngitis Pulmonary events (inflammatory processes of varying histopathology and/or fibrosis)[10]	
Gastrointestinal disorders				
Diarrhoea Nausea	Vomiting Dyspepsia Dry mouth	Dysphagia Gastrointestinal haemorrhage[11]	Oesophageal pain	
Hepato-biliary disorders				
			Idiosyncratic hepatitis	
Skin and subcutaneous tissue disorders				
	Rash[12] Urticaria Pruritus Hyperhidrosis	Alopecia Increased tendency to bruise Cold sweat	Angioedema Ecchymosis Photosensitivity reaction Purpura Erythema multiforme Stevens-Johnson syndrome Toxic Epidermal Necrolysis (Lyell Syndrome)	Erythromelalgia
Musculoskeletal and connective tissue disorders				
	Arthralgia	Muscle twitching	Myalgia	
Renal and urinary disorders				
	Frequent urination[13]	Dysuria	Urinary retention Micturition disorder	
Reproductive system and breast disorders				
	Gynaecological bleeding[14] Erectile dysfunction Ejaculation disorder[15]	Sexual dysfunction	Galactorrhoea Hyperprolactinaemia Priapism	Postpartum haemorrhage[16]
General disorders and administration site conditions				

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 behavior, suicidal ideation, suicide attempt, morbid thoughts, self-injurious behavior. 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 hemorrhage, diarrhea hemorrhagic, 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 behavior 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).

Pediatric population (see sections 4.4 and 5.1)

Adverse reactions have been observed specifically or with a different frequency in this population are described below. Frequencies for these events are based on pediatric clinical trial exposures (n = 610).

In pediatric clinical trials, suicide-related behaviors (suicide attempt and suicidal thoughts), hostility (the events reported were: anger, irritability, aggression, agitation, activation syndrome), manic reactions, including mania and hypomania (no prior episodes reported in these patients) and epistaxis, were more frequently observed among children and adolescents treated with antidepressants compared to those treated with placebo.

Isolated cases of growth retardation have been reported from clinical use (see also section 5.1).

In pediatric clinical trials, fluoxetine treatment was associated with a decrease in alkaline phosphatise levels.

Isolated cases of adverse events potentially indicating delayed sexual maturation or sexual dysfunction has been reported from pediatric clinical use (see also section 5.3).

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorization 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.

Mechanism of action
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$_1$; 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.

Major depressive episodes (children and adolescents): Clinical trials in children and adolescents aged 8 years and above have been conducted versus placebo. Fluoxetine, at a dose of 20 mg, has been shown to be significantly more effective than placebo in two short-term pivotal studies, as measured by the reduction of Childhood Depression Rating Scale-Revised (CDRS-R) total scores and Clinical Global Impression of Improvement (CGI-I) scores. In both studies, patients met criteria for moderate to severe MDD (DSM-III or DSM-IV) at three different evaluations by practicing child psychiatrists. Efficacy in the fluoxetine trials may depend on the inclusion of a selective patient population (one that has not spontaneously recovered within a period of 3-5 weeks and whose depression persisted in the face of considerable attention).
There is only limited data on safety and efficacy beyond 9 weeks. In general, efficacy of fluoxetine was modest. Response rates (the primary endpoint, defined as a 30% decrease in the CDRS-R score) demonstrated a statistically significant difference in one of the two pivotal studies (58% for fluoxetine versus 32% for placebo, P=0.013; and 65% for fluoxetine versus 54% for placebo, P=0.093). In these two studies, the mean absolute changes in CDRS-R from baseline to endpoint were 20 for fluoxetine versus 11 for placebo, P=0.002; and 22 for fluoxetine versus 15 for placebo, P<0.001.

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.

Metabolism
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

metabolized by the polymorphic enzyme CYP2D6. Fluoxetine is primarily metabolized 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 half-lives 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.

At-risk populations

Elderly: Kinetic parameters are not altered in healthy elderly when compared to younger subjects.

Children and adolescents: The mean fluoxetine concentration in children is approximately 2-fold higher than that observed in adolescents and the mean norfluoxetine concentration 1.5-fold higher. Steady-state plasma concentrations are dependent on body weight and are higher in lower weight children (see section 4.2).
As in adults, fluoxetine and norfluoxetine accumulated extensively following multiple oral dosing; steady state concentrations were achieved within 3 to 4 weeks of daily dosing.

Hepatic insufficiency: 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.

Renal insufficiency: 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 pediatric patients. At 3 mg/kg/day, plasma levels achieved in animals were approximately 0.04 to 0.5 fold (fluoxetine) and 0.3 to 2.1 fold (norfluoxetine) those usually achieved in pediatric 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 behavior 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.

7. Marketing authorization holder

Unipharm ltd, 1 Shevet Shimon St. P.O. Box 16545, , Tel Aviv, 6116401, Israel.

Manufacturer: Unipharm Ltd., "Mevo Carmel" Industrial Park.

8. Marketing authorization number(s)

162 93 35206 00

Revised in August 2024.