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Order of Ministry of
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AMMENDED
Order of Ministry of
Healthcare of Ukraine
28.10.2021 № 2374

INSTRUCTION
for medical use

FLUTISAL®

Composition:
active substance: fluoxetine;
Each hard gelatin capsule contains fluoxetine hydrochloride equivalent to fluoxetine 20 mg;
excipients: maize starch, sodium starch glycolate (type A), talc, magnesium stearate, hard gelatin capsule shell;
hard capsule shell composition: titanium dioxide (E 171), iron oxide yellow (E 172), gelatin, purified water.

Pharmaceutical form. Hard capsules.
General physical-chemical properties: size "2" hard gelatin capsule, with opaque yellow cap and opaque white body, filled with white-to-off-white granular powder.

Pharmacotherapeutic group. Antidepressants. Selective serotonin reuptake inhibitors. Fluoxetine.
ATC code: N06A B03.

Pharmacological properties.
Pharmacodynamics.
Mechanism of action.
Fluoxetine is a selective inhibitor of neuronal 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.
Pharmacokinetics.
Absorption
Fluoxetine is well absorbed from the gastrointestinal 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.

Special populations

Elderly.

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

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.

Clinical particulars.

Indications.

Major depressive episodes.

Obsessive-compulsive disorder.

Bulimia nervosa: fluoxetine is indicated as a complement of psychotherapy for the reduction of binge-eating and for purging activity.

Contraindications.

Hypersensitivity to fluoxetine or to any of the drug excipients.

Fluoxetine is contraindicated in combination with a non-selective irreversible monoamine oxidase inhibitors (e.g. iproniazid).

Fluoxetine is contraindicated in combination with metoprolol used in cardiac failure.

Drug interactions and other types of interactions.

Half-life.

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

Contraindicated combinations.

Non-selective irreversible monoamine oxidase inhibitors (e.g. iproniazid).

Some cases of serious and sometimes fatal reactions have been reported in patients receiving a selective neuronal serotonin reuptake inhibitor (SSRI) in combination with a non-selective irreversible 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 of fluoxetine with a non-selective irreversible 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 contraindicated in combination with a non-selective irreversible MAOI (see "Contraindictaions" section). Because of the two weeks-lasting effect of the latter, treatment of fluoxetine should only be started 2 weeks after discontinuation of a non-selective irreversible MAOI. Similarly, at least 5 weeks should elapse after discontinuing fluoxetine treatment before starting a non-selective irreversible 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 "Contraindictaions" section).
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 "Special warnings and precautions for use" section).
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 is present. If concomitant use of these active substances with fluoxetine cannot be avoided, a close clinical monitoring should be undertaken and the concomitant agents should be initiated at the lower recommended doses (see "Special warnings and precautions for use" section).
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 phenytoin blood levels have been observed when combined with fluoxetine. In some cases manifestations of toxicity have occurred. Consideration should be given to using titration schedules of the concomitant drug and to monitoring clinical status of patients.
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 "Special warnings and precautions for use" section).
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, pentamidine), anti-malaria treatment particularly halofantrine, certain antihistamines (astemizole, mizolastine),

should be used with caution (see "Special warnings and precautions for use", "Overdose" and "Adverse reactions" sections).
Drugs affecting haemostasis (oral anticoagulants, whatever their mechanism, platelets antiaggregants including aspirin and NSAIDs).
There is a 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 "Special warnings and precautions for use" and "Adverse reactions" sections).
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 "Adverse reactions" section).
Drugs lowering the epileptogenic threshold.
Seizures are an undesirable effect of fluoxetine. Use in combination with other agents which may lower the seizure threshold (e.g., tricyclic antidepressants, other SSRIs, phenothiazines, butyrophenones, mefloquine, chloroquine, bupropion, tramadol) may lead to an increased seizure 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, propafenone and nebivolol), and also with atomoxetine, carbamazepine, tricyclic antidepressants and risperidone. Therapy with such drugs should be started with the lowest recommended dose, or be adjusted to it. This may also apply if fluoxetine has been taken in the previous 5 weeks.

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 (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 fluoxetine 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, or 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. Therefore, they should receive careful monitoring during treatment.
A meta-analysis of placebo-controlled clinical trials of antidepressant 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 fluoxetine therapy especially in early treatment and following dose changes. Patients (and caregivers of patients) should be warned about the need to monitor the patient's condition and to seek medical

advice immediately, in the event of any worsening of the course of the disease, occurrence of suicidal behavior or thoughts or unusual changes in behavior.

Cardiovascular effects.

Cases of QT interval prolongation and ventricular arrhythmia, including *torsade de pointes* have been reported during the post-marketing period (see "Drug interactions and other types of interactions", "Adverse reactions", and "Overdose" sections).

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 and hypomagnesemia, bradycardia, acute myocardial infarction or uncompensated heart failure);
- increased exposure to fluoxetine (e.g., hepatic impairment);
- concomitant use with medicinal products known to induce QT prolongation and/or *torsade de points* (see "Drug interactions and other types of interactions" section).

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.

Non-selective irreversible monoamine oxidase inhibitors (e.g., iproniazide).

Some cases of serious and sometimes fatal reactions have been reported in patients receiving selective serotonin reuptake inhibitors (SSRI) in combination with a non-selective irreversible 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 non-selective irreversible 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 contraindicated in combination with a non-selective irreversible MAOI (see "Contraindications" section). 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 with fluoxetine, particularly when given in combination with other serotonergic (among others, L-tryptophan) and/or neuroleptic drugs (see "Drug interactions and other types of interactions" section). As these syndromes may result in potentially life-threatening conditions, treatment with fluoxetine should be discontinued if such events (characterised by clusters of symptoms, such as hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, mental status changes, including confusion, 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.

Haemorrhage.

There have been reports of skin ecchymosis and purpura with SSRIs. 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

SSRIs, particularly in concomitant use with oral anticoagulants, drugs known to affect platelet function (e.g., atypical antipsychotics, such as clozapine, phenothiazines, most tricyclic antidepressants, acetylsalicylic acid, NSAIDs), or other drugs that may increase risk of bleeding, as well as in patients with a history of bleeding disorders (see "Drug interactions and other types of interactions" section).

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. Patients with controlled epilepsy should be carefully monitored (see "Drug interactions and other types of interactions" section).

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 "Drug interactions and other types of interactions" section).

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 glycaemic control. Hypoglycaemia has occurred during therapy with fluoxetine. Hyperglycaemia has developed following discontinuation. Insulin and/or oral hypoglycaemic agents 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 (creatinine clearance <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 etiology 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 "Adverse reactions" section). 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, although in some people they may last 2–3 months or more. It is therefore advised that fluoxetine should be gradually tapered when discontinuing treatment over a period of at least one to two weeks, according to the patient's needs.

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 "Adverse reactions" section). There have been reports of long-lasting sexual dysfunction where the symptoms have continued despite discontinuation of SSRI/SNRI.

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, particular 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 "Posology and method of administration" section). 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).

Breast-feeding

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

Fertility

Animal data have shown that fluoxetine may affect sperm quality.

Human case reports with some SSRIs have shown that an effect on sperm quality is reversible.

Impact on human fertility has not been observed so far.

Effects on ability to drive and use machines.

Fluoxetine has no or negligible influence on the reaction rate when driving or operating machinery. Although fluoxetine has been shown not to affect psychomotor performance in healthy volunteers, any psychoactive drug may impair judgment 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 by fluoxetine.

Posology and method of administration.
Use orally as one or more divided doses, during or between meals.
Major depressive episodes.
A dose of 20 mg/day is recommended. Dosage should be reviewed and adjusted if necessary, within 3 to 4 weeks of initiation of therapy and thereafter as judged clinically appropriate. Although there may be an increased potential for undesirable effects at higher doses, in some patients, with insufficient response to 20 mg, the dose may be increased gradually up to a maximum of 60 mg. Dosage adjustments should be made carefully on an individual patient basis. Maintenance therapy should be given at the lowest effective dose.
Patients with depression should be treated for a sufficient period of at least 6 months to ensure that they are free from symptoms.
Obsessive-compulsive disorder (OCD)
A dose of 20 mg/day is recommended. Although there may be an increase in the potential of side effects at higher doses, in some patients, if after two weeks there is insufficient response to 20 mg, the dose may be increased gradually up to a maximum of 60 mg per day.
If no improvement is observed within 10 weeks, treatment with fluoxetine should be reconsidered. If a good therapeutic response has been obtained, fluoxetine treatment can be continued at a dosage adjusted on an individual basis. Although there is no recommendation on the duration of therapy, given that OCD is a chronic disease, it is reasonable to consider its continuation beyond 10 weeks of treatment in those patients who have received a sufficient clinical response. Dosage adjustments should be made carefully on an individual patient basis. Maintenance therapy should be given at the lowest effective dose. The need for treatment should be reassessed periodically. There are recommendations for concomitant use of behavioral psychotherapy in patients with an adequate clinical response to pharmacotherapy.
Long-term efficacy (more than 24 weeks) has not been demonstrated in OCD.
Bulimia nervosa.
A dose of 60 mg/day is recommended. Long-term efficacy (more than 3 months) has not been demonstrated in patients with bulimia nervosa.
General recommendations.
The recommended dose may be increased or decreased. Doses above 80 mg/day have not been systematically evaluated.
Elderly patients.
Caution is recommended when increasing the dose. 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.
Withdrawal symptoms.
Abrupt fluoxetine discontinuation should be avoided. If fluoxetine therapy is to be discontinued 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. 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.
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 with fluoxetine.

Children.
Do not use in children.

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 to cardiac arrest (including sinus arrhythmia and ventricular arrhythmias) or ECG changes indicative of QTc prolongation to cardiac arrest (including rare cases of *torsade 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.
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.

Adverse reaction.
The most common adverse reactions reported during fluoxetine treatment were headache, nausea, insomnia, fatigue, and diarrhea. The intensity and frequency of adverse reactions may decrease with continued treatment and do not generally lead to cessation of therapy.
The table below shows the adverse reactions observed in adult patients treated with fluoxetine. Some of these adverse reactions are common to other SSRIs. The frequency of their occurrence is defined as follows: very common (≥1/10), common (from ≥1/100 to <1/10), uncommon (from ≥1/1000 to <1/100), rare (from ≥1/10000 to <1/1000).

Very common	**Common**	**Uncommon**	**Rare**
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	Depersonalisation Elevated mood Euphoric mood	Hypomania Mania Hallucinations

	Tension Decreased libido[3] Sleep disorder Abnormal dreams[4]	Abnormal thinking Abnormal orgasm[5] Bruxism Suicidal thoughts and behavior[6]	Agitation Panic attacks Confusion Dysphemia Aggression
Nervous system disorders			
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
Eye disorders			
	Blurred vision	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	Pharyngitis Inflammatory processes of varying histopathology and/or fibrosis in the lungs[10]
Gastrointestinal disorders			
Diarrhoea Nausea	Vomiting Dyspepsia Dry mouth	Dysphagia, Gastrointestinal haemorrhage[11]	Esophageal pain
Hepatobiliary disorders			
			Idiosyncratic hepatitis
Skin and subcutaneous tissue disorders			
	Rash[2] 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)

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	Galactorrhea Hyperprolactinemia Priapism
General disorders and administration site conditions			
Fatigue[16]	Feeling jittery Chills	Malaise Feeling abnormal Feeling cold Feeling hot	Bleeding of mucous membranes
Investigations			
	Decreased weight	Increased transaminases Increased gamma-glutamyltransferase	

[1] Including anorexia.
[2] Including early morning awakening, initial insomnia, middle insomnia.
[3] Including loss of libido.
[4] Including nightmares.
[5] Including anorgasmia.
[6] Including 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] Including hypersomnia, sedation.
[8] Based on ECG measurements from clinical trials.
[9] Including hot flush.
[10] Including atelectasis, interstitial lung disease, pneumonitis.
[11] Including most frequently gingival bleeding, haematemesis, haematochezia, rectal haemorrhage, haemorrhagic diarrhoea, melaena, and gastric ulcerhaemorrhage.
[12] Including erythema, exfoliative rash, heat rash, rash, erythematous rash, follicular rash, generalized rash, macular rash, rash macular-papular, morbilliform rash, papular rash, pruritic rash, vesicular rash, umbilical erythema rash.
[13] Including pollakiuria.
[14] Including cervix haemorrhage, uterine dysfunction, uterine bleeding, genital haemorrhage, menometrorhagia, menorrhagia, metrorrhagia, polymenorrhea, postmenopausal haemorrhage, uterine haemorrhage, vaginal haemorrhage.
[15] Including ejaculation failure, ejaculation dysfunction, premature ejaculation, delayed ejaculation, retrograde ejaculation.
[16] Including asthenia.

c) Description of individual adverse reactions

Suicidal thoughts/behavior or clinical worsening.

Cases of suicidal thoughts and suicide attempts have been reported during fluoxetine therapy or immediately after discontinuation of treatment (see “Special warnings and precautions for use” section).

Bone fractures.
An increased risk of bone fractures is observed in patients receiving serotonin reuptake inhibitors and tricyclic antidepressants. The mechanism of this risk is unknown.
Withdrawal symptoms.
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 both severe and prolonged (see "Special warnings and precautions for use" section). It is therefore advised that when fluoxetine treatment is no longer required, gradual discontinuation by dose tapering should be carried out.

Shelf life.
2 years.

Storage.
Store at temperature below 25°C.
Keep out of reach of children.

Package.
10 capsules in a blister, 3 or 6 blisters in a cardboard package.

Conditions of supply.
By prescription.

Manufacturer.
KUSUM HEALTHCARE PVT LTD.

Address.
SP-289 (A), RIICO Industrial area, Chopanki, Bhiwadi, Dist. Alwar (Rajasthan), India.

Last revision date.