SUMMARY OF PRODUCT CHARACTERISTICS

1. Name of the medicinal product

Fluoxetine 20 mg Capsules

2. Qualitative and quantitative composition

Each capsule containsFluoxetine Hydrochloride equivalent to Fluoxetine BP/EP 20 mg

For the full list of excipients, see section 6.1.

3. Pharmaceutical form

Capsules

Green/Off-white hard gelatin self-locked capsules of size '2'
imprinted with 'FLX' and 'MIL' on cap/body in black edible ink
containing white powder.

4. Clinical particulars

4.1 Therapeutic indications

Adults:

Major depressive episodes.

Obsessive-compulsive disorder.

Bulimia nervosa: Fluoxetine 20mg Capsules 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

Posology

Adults

Major Depressive Episodes–

Adults and the elderly: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 20mg, the dose may be increased gradually up to a maximum of 60mg (see section 5.1). Dosage adjustments should be made carefully on an individual patient basis, to maintain the patients 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:

Adults and the elderly:

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 20mg, the dose may be increased gradually up to a maximum of 60mg.

If no improvement is observed within 10 weeks, treatment with fluoxetine should be reconsidered. If a good therapeutic response has been obtained, treatment can be continued at a dosage adjusted on an individual basis. While there are no systematic studies to answer the question of how long to continue fluoxetine treatment, OCD is a chronic condition and it is reasonable to consider continuation beyond 10 weeks in responding patients. Dosage adjustments should be made carefully on an individual patient basis, to maintain the patient at the lowest effective dose. The need for treatment should be reassessed periodically. Some clinicians advocate concomitant behavioural psychotherapy for patients who have done well on pharmacotherapy.

Long-term efficacy (more than 24 weeks) has not been demonstrated in OCD.

Bulimia nervosa: Adults and the elderly: A dose of 60 mg/day is recommended. Long-term efficacy (more than 3 months) has not been demonstrated in bulimia nervosa.

All indications: The recommended dose may be increased or decreased. Doses above 80mg/day have not been systematically evaluated.

Paediatric 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 10mg/day given as 2.5ml of the Fluoxetine oral 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 20mg/day. Clinical trial experience with daily doses greater than 20mg 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 paediatric 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 40mg. Maximum recommended dose is 60mg/day.

Hepatic impairment

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

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.

The capsule and oral solution forms are bioequivalent.

4.3 Contraindications

Fluoxetine is contra-indicated in combination with irreversible, non-selective monoamine oxidase inhibitors (e.g. iproniazid).

Fluoxetine is contra-indicated in combination with metoprolol used in cardiac failure.

4.4 Special warnings and precautions for use

Paediatric population - Children and adolescents under 18 years of age

Fluoxetine 20mg Capsules 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.

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.

Cardiovascular Effects

Cases of QT interval prolongation and ventricular arrhythmia including torsades de pointes have been reported during the post-marketing period.

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.

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).

Fluoxetine is contra-indicated in combination with 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.

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 cutaneous bleeding abnormalities such as ecchymosis and purpura with SSRI's.

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.

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.

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..

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 aetiologycannot be identified, fluoxetine should be discontinued.

Mydriasis

Mydriasishas 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.

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 when considering pharmacodynamic or pharmacokinetic drug interactions (e.g., when switching from fluoxetine to other antidepressants).

Contra-indicated combinations

Fluoxetine is contra-indicated in combination with an irreversible, non-selective MAOI . 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.

Not recommended combinations

Tamoxifen: 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.

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.

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.

Serotoninergic drugs (lithium, tramadol, triptans, tryptophan, selegiline (MAOI-B), St. John's Wort (Hypericumperforatum)): 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.

QT interval prolongation: 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.

Drugs affecting haemostasis (oral anticoagulants, whatever their mechanism, platelets antiaggregants including aspirin and NSAIDs): risk of increased bleeding.

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.

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, 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.

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. 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 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

Fluoxetine 20mg Capsules 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. <u>Tabulated list of adverse reactions</u>

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**	**Very Rare**	**Frequency Not Known**
Blood and lymphatic system disorders					
			Thrombocytopenia Leucopenia Neutropenia		
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 behaviour [6]	Hypomania Mania Hallucinations Agitation Panic attacks Confusion Dysphemia Aggression		
Nervous system disorders					
Headache	Disturbance in attention Dizziness Dysgeusia Lethargy Somnolence[7]	Psychomotor hyperactivity Dyskinesia Ataxia Balance disorder Myoclonus	Convulsion Akathisia Buccoglossal syndrome Serotonin syndrome		

	Tremor	Memory impairment			
Eye disorders					
	Vision blurred	Mydriasis			
Ear and labyrinth disorders					
		Tinnitus			
Cardiac disorders					
	Palpitations Electrocardio-gram QT prolonged QTcF ≥450 msec)[8]		Ventricular arrhythmia including torsade de pointes		
Vascular disorders					
	Flushing[9]	Hypotension	Vasculitis Vasodilatation		
Respiratory, thoracic and mediastinal disorders					
	Yawning	Dyspnoea Epistaxis	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)		
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		
General disorders and administration site conditions					
Fatigue[16]	Feeling jittery Chills	Malaise Feeling abnormal Feeling cold Feeling hot	Mucosal haemorrhage		
Investigations					
	Weight decreased	Transaminases increased and Gamma-glutamyltransferase increased			

Includes anorexia

Includes early morning awakening, initial insomnia, middle insomnia

Includes loss of libido

Includes nightmares

Includes anorgasmia

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

Includes hypersomnia, sedation

Based on ECG measurements from clinical trials

Includes hot flush

Includes atelectasis, interstitial lung disease, pneumonitis

Includes most frequently gingival bleeding, haematemesis, haematochezia, rectal haemorrhage, diarrhoea haemorrhagic, melaena, and gastric ulcerhaemorrhage

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

Includes pollakiuria

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

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

Includes asthenia

c Paediatric population :

In paediatric clinical trials, suicide-related behaviours (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 commonly reported and were more frequently observed among children and adolescents treated with antidepressants compared to those treated with placebo.

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.

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.

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.

Biotransformation

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 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.

5.3 Preclinical safety data
There is no evidence of carcinogenicity or mutagenicity from *in vitro* or animal studies.

6. Pharmaceutical particulars

6.1 List of excipients

The other ingredient is Pregelatinised maize starch. The capsule shell contains: E171, E133 and E172 andGelatin. The printing ink contains:Shellac, Propylene Glycol and Black iron oxide.

6.2 Incompatibilities
Not applicable

6.3 Shelf life
3 years.

6.4 Special precautions for storage
Store below 25ºC. Protect from moisture.

6.5 Nature and contents of container
Al/PVC blisters. Pack size 3 x10 capsules

6.6 Special precautions for disposal and other handling
No special requirements.

7. Marketing authorisation holder

Milan Laboratories (India) Pvt. Ltd.
303 & 304, Odyssey IT park,
Road No. 9, Opposite MIDC Office,
Wagle Estate, Thane -400604
India
Tel No. 91-22-6159 7733
Fax No. 91-22-25877736
email : info@milanlabs.com
web site : www.milanlabs.com

8. Marketing authorisation number(s)

To be allotted

9. Date of first authorisation/renewal of the authorisation

To be allotted

10. Date of revision of the text

To be allotted

1.7.2. Labelling (immediate and outer label)

Enclosed.

1.7.3. Patient Information Leaflet (PIL) or package Insert

Name of the medicinal product

Fluoxetine 20mg Capsules

2. Qualitative and quantitative composition

Each capsule contains 20 mg of Fluoxetine (as fluoxetine hydrochloride EP/BP).

Excipient: Pregelatinised Maize Starch BP

3. Pharmaceutical form

Green/Off-white hard gelatin self-locked capsules of size '2' imprinted with 'FLX' and 'MIL' on cap/body in black edible ink containing white powder

4. Clinical particulars

4.1 Therapeutic indications
Adults:

Major depressive episodes.

Obsessive-compulsive disorder.

Bulimia nervosa: Fluoxetine 20mg Capsules 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
Posology

Adults

Major depressive episodes

Adults and the elderly: The recommended dose is 20mg daily. Dosage should be reviewed and adjusted if necessary, within 3 to 4 weeks of initiation of therapy and thereafter as judged clinically appropriate. Dosage adjustments should be made carefully on an individual patient basis, to maintain the patients 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

Adults and the elderly: The recommended dose is 20mg daily. Although there may be an increased potential for undesirable effects at higher doses, in some patients, if after two weeks there is insufficient response to 20mg, the dose may be increased gradually up to a maximum of 60mg.

Bulimia nervosa: Adults and the elderly: A dose of 60mg/day is recommended. Long-term efficacy (more than 3 months) has not been demonstrated in bulimia nervosa.

All indications: The recommended dose may be increased or decreased. Doses above 80mg/day have not been systematically evaluated.

Paediatric 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 10mg/day given as 2.5ml of the Fluoxetine oral 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 20mg/day. *Lower-weight children:* Due to higher plasma levels in lower-weight children, the therapeutic effect may be achieved with lower doses Forpaediatric 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 40mg. Maximum recommended dose is 60mg/day.

Hepatic impairment

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

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

Fluoxetine is contra-indicated in combination with irreversible, non-selective monoamine oxidase inhibitors (e.g. iproniazid).

Fluoxetine is contra-indicated in combination with metoprolol used in cardiac failure.

4.4 Special warnings and precautions for use

Paediatric population - Children and adolescents under 18 years of age

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Suicide/suicidal thoughts or clinical worsening

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Cardiovascular Effects

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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.

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.

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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).

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There have been reports of cutaneous bleeding abnormalities such as ecchymosis and purpura with SSRI's.

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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.

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.

Akathisia/psychomotor restlessness

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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..

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 aetiologycannot be identified, fluoxetine should be discontinued.

Mydriasis

Mydriasishas 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.

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 when considering pharmacodynamic or pharmacokinetic drug interactions (e.g., when switching from fluoxetine to other antidepressants).

Contra-indicated combinations

Fluoxetine is contra-indicated in combination with an irreversible, non-selective MAOI . 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.

Not recommended combinations

Tamoxifen: 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.

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.

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.

Serotoninergic drugs (lithium, tramadol, triptans, tryptophan, selegiline (MAOI-B), St. John's Wort (Hypericumperforatum)): 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.

QT interval prolongation: 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.

Drugs affecting haemostasis (oral anticoagulants, whatever their mechanism, platelets antiaggregants including aspirin and NSAIDs): risk of increased bleeding.

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.

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, 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.

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. 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 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

Fluoxetine 20mg Capsules 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**
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 behaviour [6]	Hypomania Mania Hallucinations 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			
	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	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)
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
General disorders and administration site conditions			
Fatigue[16]	Feeling jittery Chills	Malaise Feeling abnormal Feeling cold Feeling hot	Mucosal haemorrhage
Investigations			
	Weight decreased	Transaminases increased Gamma-glutamyltransferase increased	

[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, diarrhoeahaemorrhagic, 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] Includes asthenia

c. Paediatric population

In paediatric clinical trials, suicide-related behaviours (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 commonly reported and were more frequently observed among children and adolescents treated with antidepressants compared to those treated with placebo.

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.

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.

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.

Biotransformation

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 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.

5.3 Preclinical safety data

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

6. Pharmaceutical particulars

6.1 List of excipients

The other ingredient is Pregelatinised maize starch. The capsule shell contains: E171, E133 and E172 andGelatin. The printing ink contains:Shellac, Propylene Glycol and Black iron oxide.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Capsules: 3 years.

6.4 Special precautions for storage

Store below 30^{o}C. Protect from moisture.

6.5 Nature and contents of container
Capsules: PVC/aluminium blister packs of 3 x 10's.

6.6 Special precautions for disposal and other handling
No special requirements.

7. Marketing authorisation holder

Milan Laboratories (India) Pvt. Ltd.

303 & 304, Odyssey IT park,

Road No. 9, Opposite MIDC Office,
Wagle Estate, Thane -400604
India
E-mail: info@milanlabs.com

8. Number(S) in The National Register of Finished Pharmaceutical Products

07228/08569/NMR/2020

9. Date of First Authorisation/Renewal of the Authorisation

31.03.2022

10. Date of Revision of the text

07.07.2023