AGOG Pharma Ltd.
(WHO - GMP CERTIFIED - GOVT RECOGNISED EXPORT HOUSE)
Regd. Office & Factory : Plot No. 33, Sector II, The Vasai Taluka Industrial Co-op. Estate Ltd. Gauraipada, Vasai (E), Dist. Thane - 401 208. INDIA.
Tel. : 95250 - 2455801 / 2452714 / 2453525 • Fax : 95250 - 2452074 (0091 - 250 - 2452074) • Email : agog@vsnl.net & agogpharma@rediffmail.com

1.5 PRODUCT INFORMATION

1.5.1 Prescribing Information (Summary of Products Characteristics)

1. NAME OF DRUG PRODUCT

1. Name of drug product

FLUOXETINE HYDROCHLORIDE USP EQUIVALENT TO FLUOXATINE 20 MG TABLETS

1.1 (Trade) name of product

FLUOXETINE TABLETS USP 20 MG

1.2 Strength

Each film tablet contains:
Fluoxetine hydrochloride USP equivalent to Fluoxatine 20 mg

1.3 Pharmaceutical Dosage Form

Film coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITIONS

2.1 Qualitative Declaration

Each film tablet contains:
Fluoxetine hydrochloride USP equivalent to Fluoxatine 20 mg

2.2 Quantitative Declaration

Ingredients	Specification	Label Claim	Qty. / Tab.
ACTIVE			
Fluoxetine hydrochloride USP equivalent to Fluoxatine	USP	20.0 mg	22.800 mg
NON ACTIVE			
Micro Crystalline Cellulose powder	BP	-	90.00 mg
Maize starch (10% extra added to compensate LOD.)	BP	-	68.00 mg
Isopropyl alcohol	BP	-	65.00 mg
Poly Vinyl Pyrrolidone	BP	-	4.000 mg
Talcum	BP	-	3.000 mg
Magnesium stearate	BP	-	2.000 mg
Cross Carmellose Sodium	BP	-	4.000 mg
Polyplasdone XL-10	USP	-	2.000 mg
Colloidal Silicon Dioxide	BP	-	1.000 mg
Methylene Dichloride	BP	-	43.00 mg
Iso propyl Alcohol	BP	-	29.00 mg
Colour Instacoat Sol White 010	BP	-	3.800 mg

USP = United State Pharmacopoeia.
BP = British Pharmacopoeia.

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3. PHARMACEUTICAL DOSAGE FORM

Film Coated tablets

White, circular, biconvex film coated tablets.

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4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

Fluoxetine is a selective serotonin reuptake inhibitor indicated for both acute and maintenance treatment of major depressive disorder, obsessive compulsive disorder, and bulimia nervosa; however, it is only indicated for acute treatment of panic disorder independent of whether agoraphobia is present. Fluoxetine may also be used in combination with olanzapine to treat depression related to Bipolar I Disorder and treatment resistant depression.

4.2 Posology and Method of Administration

Indication	Adult	Pediatric
Major Depressive Disorder	20 mg/day in am (initial dose)	10 to 20 mg/day (initial dose)
Obsessive Compulsive Disorder	20 mg/day in am (initial dose)	10 mg/day (initial dose)
Bulimia Nervosa	60 mg/day in am	-
Panic Disorder	10 mg/day (initial dose)	-
Depressive Episodes Associated with Bipolar I Disorder	Oral in combination with olanzapine: 5 mg of oral olanzapine and 20 mg of fluoxetine once daily (initial dose)	-
Treatment Resistant Depression	Oral in combination with olanzapine: 5 mg of oral olanzapine and 20 mg of fluoxetine once daily (initial dose)	-

- Consider tapering the dose of fluoxetine for pregnant women during the third trimester.
- A lower or less frequent dosage should be used in patients with hepatic impairment, the elderly, and for patients with concurrent disease or on multiple concomitant medications.
- Dosing with Fluoxetine Weekly - initiate 7 days after the last daily dose of Fluoxetine 20 mg.
- Fluoxetine monotherapy is not indicated for the treatment of Depressive Episodes associated with Bipolar I Disorder or treatment resistant depression.

4.3 Contraindications

- Do not use with an MAOI or within 14 days of discontinuing an MAOI due to risk of drug interaction. At least 5 weeks should be allowed after stopping Fluoxetine before treatment with an MAOI.
- Do not use with pimozide due to risk of drug interaction or QTc prolongation.
- Do not use with thioridazine due to QTc interval prolongation or potential for elevated thioridazine plasma levels. Do not use thioridazine within 5 weeks of discontinuing Fluoxetine.
- When using Fluoxetien and olanzapine in combination, also refer to the Contraindications section of the package insert for Symbyax

4.4 Special Warnings and Precautions for Use

- Clinical Worsening and Suicide Risk: Monitor for clinical worsening and suicidal thinking and behavior.
- Serotonin Syndrome or Neuroleptic Malignant Syndrome (NMS)-like Reactions: Have been reported with Fluoxetine. Discontinue Fluoxetine and initiate supportive treatment.
- Allergic Reactions and Rash: Discontinue upon appearance of rash or allergic phenomena.
- Activation of Mania/Hypomania: Screen for Bipolar Disorder and monitor for mania/hypomania.
- Seizures: Use cautiously in patients with a history of seizures or with conditions that potentially lower the seizure threshold.
- Altered Appetite and Weight: Significant weight loss has occurred.
- Abnormal Bleeding: May increase the risk of bleeding. Use with NSAIDs, aspirin, warfarin, or drugs that affect coagulation may potentiate the risk of gastrointestinal or other bleeding.
- Hyponatremia: Has been reported with Fluoxetine in association with syndrome of inappropriate antidiuretic hormone (SIADH).
- Anxiety and Insomnia: May occur.
- Potential for Cognitive and Motor Impairment: Has potential to impair judgment, thinking, and motor skills. Use caution when operating machinery.
- Long Half-Life: Changes in dose will not be fully reflected in plasma for several weeks.
- Fluoxetine and Olanzapine in Combination: When using Fluoxetine and olanzapine in combination, also refer to the Warnings and Precautions section of the package insert for Symbyax.

4.5 Interaction with Other Drugs, Other Forms of Interactions

- Monoamine Oxidase Inhibitors (MAOI): Fluoxetine is contraindicated for use with MAOI's, or within 14 days of discontinuing an MAOI due to risk of drug interaction. At least 5 weeks should be allowed after stopping Fluoxetine before starting treatment with an MAOI.
- Pimozide: Fluoxetine is contraindicated for use with pimozide due to risk of drug interaction or QTc prolongation.
- Thioridazine: Fluoxetine is contraindicated for use with thioridazine due to QTc interval prolongation or potential for elevated thioridazine plasma levels. Do not use thioridazine within 5 weeks of discontinuing Fluoxetine.
- Drugs Metabolized by CYP2D6: Fluoxetine is a potent inhibitor of CYP2D6 enzyme pathway.
- Tricyclic Antidepressants (TCAs): Monitor TCA levels during co-administration with Fluoxetine or when Fluoxetine has been recently discontinued.
- CNS Acting Drugs: Caution should be used when taken in combination with other centrally acting drugs.
- Benzodiazepines: Diazepam – increased t ½ , alprazolam - further psychomotor performance decrement due to increased levels.
- Antipsycotics: Potential for elevation of haloperidol and clozapine levels.
- Anticonvulsants: Potential for elevated phenytoin and carbamazepine levels and clinical anticonvulsant toxicity.
- Serotonergic Drugs: Potential for Serotonin Syndrome.
- Triptans: There have been rare postmarketing reports of Serotonin Syndrome with use of an SSRI and a triptan.
- Tryptophan: Concomitant use with tryptophan is not recommended.
- Drugs that Interfere with Hemostasis (e.g. NSAIDs, Aspirin, Warfarin): May potentiate the risk of bleeding.

4.6 Use in Pregnancy and Lactation

- Pregnancy: PROZAC Should Be Used During Pregnancy Only If The Potential Benefit Justifies The Potential Risks To The Fetus.
- Nursing Mothers: Breast Feeding Is Not Recommended.

4.7 Adverse effects

Most common side effects reported by adults include insomnia, nausea, diarrhea, anorexia, dry mouth, headache, drowsiness, anxiety, nervousness, yawning, decreased libido, decreased arousal (seen as decreased lubrication in women and decreased erectile function in men), bruising, bleeding (rarely), hyperhidrosis, also keep in mind if this may be due to underlying mania/psychosis, seizures (rarely), induction of

mania, rare activation of suicidal ideation and behavior (especially in teenagers), weight gain/loss, decreased orgasm (anorgasmia and ejaculation latency), muscle weakness, tremors, and pharyngitis.

The 5HT2C antagonism is what is thought to contribute to the anxiety, insomnia, and agitation that patients perceive with fluoxetine. Patients may even have a panic attack with the administration with fluoxetine. Thus it is the clinician's responsibility to educate patients.

Most side effects are immediate and disappear with time. Thus, it is best to wait for the side effects to subside before altering treatment. Most side effects are dose-dependent and time-dependent. It is important to be cautious of the emergence of agitation or activation, which may indicate a bipolar state, which may require the addition of a mood stabilizer or an atypical antipsychotic. Fluoxetine can be activating, thus if insomnia is present, consider dosing early in the morning. Additionally, one may reduce the dose if side effects are too distressing for the patient. The patient should be cautioned about side effects, if they persist, after a few weeks, switching to a different antidepressant may be indicated.

It is best to try another antidepressant before relying on augmentation strategies. This approach can minimize polypharmacy and encourage adherence to psychotropic medications. Trazodone, mirtazapine, or a hypnotic may be options for insomnia. Mirtazapine may also help with agitation or gastrointestinal side effects. Benzodiazepines may treat for anxiety. Bupropion or a phosphodiesterase inhibitor (i.e., sildenafil) may address for sexual dysfunction. Bupropion may also be an option for potential cognitive slowing or apathy seen with fluoxetine.

4.8 Overdoses

Fluoxetine is rarely lethal in monotherapy overdose. However, when taken in conjunction with alcohol, it may cause ataxia and respiratory depression. The drug may cause serotonin syndrome (clinical constellation of changes in mental status, autonomic instability, and neuromuscular abnormalities) when taken in excessive amounts or if combined with other agents that also increase serotonin levels.

In the case of SSRI overdose, the goal is to provide supportive therapy. This support can be in the form of airway protection, serial ECGs to monitor for cardiotoxicity, administration of benzodiazepines for sedation, and GI decontamination with activated charcoal.

Serotonin syndrome is treatable with the administration of cyproheptadine

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5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmaco-Kinetic Properties

Absorption

- The oral bioavailability of fluoxetine is <90% as a result of hepatic first pass metabolism.
- In a bioequivalence study, the Cmax of fluoxetine 20 mg for the established reference formulation was 11.754 ng/mL while the Cmax for the proposed generic formulation was 11.786 ng/ml.
- Fluoxetine is very lipophilic and highly plasma protein bound, allowing the drug and it's active metabolite, norfluoxetine, to be distributed to the brain.

Volume of distribution

The volume of distribution of fluoxetine and it's metabolite varies between 20 to 42 L/kg.

Protein binding

Approximately 94% of fluoxetine is plasma protein bound.

Metabolism

Fluoxetine is metabolized to norfluoxetine by CYP1A2, CYP2B6, CYP2C9, CYP2C19, CYP2D6, CYP3A4, and CYP3A5 upon ingestion. Although all of the mentioned enzymes contribute to N-demethylation of fluoxetine, CYP2D6, CYP2C9 and CYP3A4 appear to be the major contributing enzymes for phase I metabolism. In addition, there is evidence to suggest that CYP2C19 and CYP3A4 mediate O-dealkylation of fluoxetine and norfluoxetine to produce para-trifluoromethylphenol which is subsequently metabolized to hippuric acid. Both fluoxetine and norfluoxetine undergo glucuronidation to facilitate excretion.

Notably, both the parent drug and active metabolite inhibit CYP2D6 isozymes, and as a result patients who are being treated with fluoxetine are susceptible to drug interactions.

Hover over products below to view reaction partners

- Fluoxetine
- Norfluoxetine
- 4-Trifluoromethylphenol
- Hippuric acid
- Norfluoxetine alcohol

- Norfluoxetine acid
- Norfluoxetineglucuronide
- 4-Trifluoromethylphenol
- Hippuric acid
- Fluoxetine glucuronide

Route of elimination

Fluoxetine is primarily eliminated in the urine.

5.2 Pharmaco-dynamic properties

Fluoxetine blocks the serotonin reuptake transporter in the presynaptic terminal, which ultimately results in sustained levels of 5-hydroxytryptamine (5-HT) in certain brain areas.[13] However, fluoxetine binds with relatively poor affinity to 5-HT, dopaminergic, adrenergic, cholinergic, muscarinic, and histamine receptors which explains why it has a far more desirable adverse effect profile compared to earlier developed classes of antidepressants such as tricyclic antidepressants

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6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

1. Micro Crystalline Cellulose powder	BP	90.00	mg
2. Maize starch (10% extra added to compensate LOD.)	BP	68.00	mg
3. Isopropyl alcohol	BP	65.00	mg
4. Poly Vinyl Pyrrolidone	BP	4.000	mg
5. Talcum	BP	3.000	mg
6. Magnesium stearate	BP	2.000	mg
7. Cross Carmellose Sodium	BP	4.000	mg
8. Polyplasdone XL-10	BP	2.000	mg
9. Colloidal Silicon Dioxide	BP	1.000	mg
10. Methylene Dichloride	BP	43.00	mg
11. Iso propyl Alcohol	BP	29.00	mg
12. Colour Instacoat Sol White 010	BP	3.800	mg

6.2 Incompatibilities

None reported

6.3 Shelf-Life

36 months from the date of manufacture.

6.4 Special Precautions for Storage

Store below 30°C.
Protect from light.

6.5 Nature and Contents of Container

Jar pack of 100 tablets
Material of construction of primary packaging material is attached.

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