ADVANCE Capsules & Liquid

ایڈوانس کیپسولز اور لیکوئڈ

COMPOSITION:

Each capsule contains: Fluoxetine HCl BP/ USP .....20 mg
Each 5 ml contains: Fluoxetine HCl BP/ USP.....20 mg

DESCRIPTION: Fluoxetine is a psychotropic drug for oral administration. It is designated (±)-N-methyl-3-phenyl-3-[(alpha,alpha,alpha- trifluoro-*p*-tolyl)oxy]propylamine hydrochloride and has the empirical formula of $C_{17}H_{18}F_3NO \cdot HCl$. Its molecular weight is 345.79.

PHARMACOLOGY: ***Pharmacodynamics:*** The antidepressant, antiobsessive compulsive, and antibulimic actions of fluoxetine are presumed to be linked to its inhibition of CNS neuronal uptake of serotonin. Fluoxetine blocks the uptake of serotonin into human platelets. Fluoxetine binds tomuscarinic, histaminergic, and alpha1-adrenergic receptors and other membrane receptors from brain tissue much less potently in vitro than do the tricyclic drugs. ***Pharmacokinetics:*** A single oral 40-mg dose produces peak plasma concentrations of fluoxetine from 15 to 55 ng/mL after 6 to 8 hours. Food does not appear to affect the systemic bioavailability of fluoxetine, although it may delay its absorption by 1 to 2 hours. Over the concentration range from 200 to 1000 ng/mL, approximately 94.5% of fluoxetine is bound in vitro to human serum proteins, including albumin and alpha1-glycoprotein. Fluoxetine is extensively metabolized in the liver to norfluoxetine and a number of other unidentified metabolites. The primary route of elimination appears to be hepatic metabolism to inactive metabolites excreted by the kidney.

INDICATIONS: ADVANCE Capsules & Liquid are indicated for the treatment of:

1. Major Depressive Disorder
2. Obsessive Compulsive Disorder
3. Bulimia Nervosa
4. Panic Disorder

CONTRAINDICATIONS:

- Fluoxetine is contraindicated in patients known to be hypersensitive to it.
- Fluoxetine should not be used in combination with an MAOI, or within a minimum of 14 days of discontinuing therapy with an MAOI. Since fluoxetine and its major metabolite have very long elimination half-lives, at least 5 weeks should be allowed after stopping Fluoxetine before starting an MAOI.
- Concomitant use in patients taking pimozide is contraindicated.
- Thioridazine should not be administered with Fluoxetine or within a minimum of 5 weeks after Fluoxetine has been discontinued.

POSSIBLE ADVERSE EFFECTS: The most commonly encountered side effects include anxiety, nervousness, insomnia, drowsiness, fatigue, asthenia, tremors, dizziness, light-headedness, dryness of the mouth, sweating, anorexia, nausea, diarrhea and pharyngitis.

DRUG INTERACTIONS: ***Drugs Metabolized by CYP2D6***: Fluoxetine inhibits the activity of CYP2D6. Coadministration of fluoxetine with other drugs that are metabolized by CYP2D6, including certain antidepressants (e.g., TCAs), antipsychotics (e.g., phenothiazines and most atypicals), and antiarrhythmics (e.g., propafenone, flecainide, and others) should be approached with caution. ***Anticonvulsants:*** Patients on stable doses of phenytoin and carbamazepine have developed elevated plasma anticonvulsant concentrations and clinical anticonvulsant toxicity following initiation of concomitant fluoxetine treatment. ***Antipsychotics:*** Elevation of blood levels of haloperidol and clozapine has been observed in patients receiving concomitant fluoxetine. The potential for drug interactions or QTc prolongation warrants restricting the concurrent use of pimozide and Fluoxetine. Due to the risk of serious ventricular arrhythmias and sudden death potentially associated with elevated plasma levels of thioridazine, it should not be administered with fluoxetine or within a minimum of 5 weeks after fluoxetine has been discontinued. ***Benzodiazepines:*** Coadministration of alprazolam and fluoxetine is associated with increased alprazolam plasma concentrations. ***Lithium:*** There have been reports of both increased and decreased lithium levels when lithium was used concomitantly with fluoxetine. Lithium levels should be monitored when these drugs are administered concomitantly. ***Monoamine Oxidase Inhibitors:*** Fluoxetine should not be used in combination with an MAOI, or within a minimum of 14 days of discontinuing therapy with an MAOI. Since fluoxetine and its major metabolite have very long elimination half-lives, at least 5 weeks should be allowed after stopping Fluoxetine before starting an MAOI. ***Serotonergic Drugs:*** The concomitant use of Fluoxetine with other SSRIs, SNRIs or tryptophan is not recommended. ***Potential Effects of Coadministration of Drugs Tightly Bound to Plasma Proteins***: Because fluoxetine is tightly bound to plasma protein, the administration of fluoxetine to a patient taking another drug that is tightly bound to protein (e.g., Coumadin, digitoxin) may cause a shift in plasma concentrations potentially resulting in an adverse effect. ***Drugs that Interfere with Hemostasis (e.g., NSAIDs, Aspirin, Warfarin):*** Patients receiving warfarin therapy should be carefully monitored when fluoxetine is initiated or discontinued because of the altered anti coagulant effect including increased bleeding.

WARNINGS: ***Clinical Worsening & Suicide Risk:*** All patients being treated with antidepressants for any indication should be monitored appropriately and observed closely for clinical worsening, suicidality, and unusual changes in behaviour, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases. ***Screening Patients for Bipolar Disorder:*** Fluoxetine is not approved for use in treating bipolar depression. ***Rash & Possibly Allergic Events:*** Anaphylactoid events, including bronchospasm, angioedema, laryngospasm, and urticaria alone and in combination, have been reported. Upon the appearance of rash or of other possibly allergic phenomena for which an alternative etiology cannot be identified, fluoxetine should be discontinued. ***Serotonin Syndrome:*** The development of a potentially life-threatening serotonin syndrome may occur with SNRIs and SSRIs, including fluoxetine treatment. The concomitant use of fluoxetine with serotonin precursors is not recommended. ***Potential Interaction with Thioridazine:*** Thioridazine administration produces a dose-related prolongation of the QTc interval, which is associated with serious ventricular arrhythmias, such as torsades de pointes-type arrhythmias, and sudden death. This risk is expected to increase with fluoxetine-induced inhibition of thioridazine metabolism. ***Abnormal Bleeding***: SSRIs and SNRIs, including fluoxetine, may increase the risk of bleeding events. Concomitant use of aspirin, nonsteroidal anti-inflammatory drugs, warfarin, and other anti-coagulants may add to this

risk. ***Altered Appetite & Weight:*** Significant weight loss, especially in underweight depressed or bulimic patients may be an undesirable result of treatment with fluoxetine. ***Hyponatremia:*** Hyponatremia may occur as a result of treatment with SSRIs and SNRIs, including fluoxetine. Elderly patients may be at greater risk of developing hyponatremia with SSRIs and SNRIs. Also, patients taking diuretics or who is otherwise volume depleted may be at greater risk. ***Seizures:*** Fluoxetine should be introduced with care in patients with a history of seizures. ***Use in Patients with Concomitant Illness:*** Caution is advisable in using fluoxetine in patients with diseases or conditions that could affect metabolism or hemodynamic responses. A lower or less frequent dosage should be used in patients with hepatic impairment. ***Interference with Cognitive & Motor Performance:*** Any psychoactive drug may impair judgment, thinking, or motor skills, and patients should be cautioned about operating hazardous machinery, including automobiles. ***Discontinuation of Treatment with Fluoxetine:*** A gradual reduction in the dose rather than abrupt cessation is recommended whenever possible. ***Pregnancy:*** Fluoxetine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. ***Lactation:*** Because fluoxetine is excreted in human milk, nursing while on Fluoxetine is not recommended. ***Pediatric Use:*** Fluoxetine is approved for use in pediatric patients with MDD and OCD. The safety and effectiveness in pediatric patients <8 years of age in major depressive disorder and <7 years of age in OCD have not been established.

DOSAGE AND ADMINISTRATION: Major Depressive Disorder: *Initial Treatment:* *Adult:* A dose of 20 mg/day (1 ADVANCE capsule or 5 ml of ADVANCE liquid), administered in the morning, is recommended as the initial dose. A dose increase may be considered after several weeks if insufficient clinical improvement is observed. Doses above 20 mg/day may be administered on a once-a-day (morning) or BID schedule (i.e., morning and noon) and should not exceed a maximum dose of 80 mg/day (4 ADVANCE capsules or 20 ml of ADVANCE liquid). *Pediatric (children and adolescents):* Treatment should be initiated with a dose of 10 or 20 mg/day (2.5 or 5 ml of ADVANCE liquid). After 1 week at 10 mg/day, the dose should be increased to 20 mg/day (5 ml of ADVANCE liquid). ***Maintenance/Continuation/Extended Treatment:*** It is generally agreed that acute episodes of major depressive disorder require several months or longer of sustained pharmacologic therapy. ***Switching Patients to a Tricyclic Antidepressant (TCA):*** Dosage of a TCA may need to be reduced, and plasma TCA concentrations may need to be monitored temporarily when ADVANCE is coadministered or has been recently discontinued. **Obsessive Compulsive Disorder: *Initial Treatment:*** *Adults:* A dose of 20 mg/day (1 ADVANCE capsule or 5 ml of ADVANCE liquid), administered in the morning, is recommended as the initial dose. Doses above 20 mg/day may be administered on a once-a-day (i.e., morning) or BID schedule (i.e., morning and noon). A dose range of 20 to 60 mg/day is recommended. The maximum dose of ADVANCE should not exceed 80 mg/day (4 ADVANCE capsules or 20 ml of ADVANCE liquid). *Pediatric (children and adolescents):* In adolescents and higher weight children, treatment should be initiated with a dose of 10 mg/day (2.5 ml of ADVANCE liquid). After 2 weeks, the dose should be increased to 20 mg/day (5 ml of ADVANCE liquid). Additional dose increases may be considered after several more weeks if insufficient clinical improvement is observed. A dose range of 20 to 60 mg/day is recommended. In lower weight children, treatment should be initiated with a dose of 10 mg/day (2.5 ml of ADVANCE liquid). ***Maintenance/Continuation Treatment:*** Dosage adjustments should be made to maintain the patient on the lowest effective dosage, and patients should be periodically reassessed to determine the need for treatment.

Bulimia Nervosa: *Initial Treatment:* *Adults:* The recommended dose is 60 mg/day (3 ADVANCE capsules or 15 ml of ADVANCE liquid), administered in the morning. ***Maintenance/Continuation Treatment:*** Patients should be periodically reassessed to determine the need for maintenance treatment.

Panic Disorder: *Initial Treatment:* *Adults:* Treatment should be initiated with a dose of 10 mg/day (2.5 ml of ADVANCE liquid). After 1 week, the dose should be increased to 20 mg/day (1 ADVANCE capsule or 5 ml of ADVANCE liquid). ADVANCE doses above 60 mg/day (3 ADVANCE capsules or 15 ml of ADVANCE liquid) have not been systematically evaluated in patients with panic disorder.

SPECIAL INSTRUCTIONS TO THE PHYSICIAN: *Discontinuation of Treatment with Fluoxetine:* A gradual reduction in the dose rather than abrupt cessation is recommended whenever possible. 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. ***Hepatic & Renal Impairment:*** Lower doses, such as alternate day dosing, have been recommended in patients with significant hepatic impairment and for patients with mild to moderate renal failure a lower or less frequent dose should be used, and in those in multiple medications. ***Overdosage:*** Fluoxetine has a wide margin of safety in overdosage and there is no specific antidote available for it. However nausea, vomiting, agitation, restlessness, hypomania and other signs of CNS excitation are prominent. In such cases, an airway should be established; vital signs, cardiac monitoring & supportive and symptomatic measures should be instituted.

STORAGE / PRECAUTIONS: Store in a cool, dry and dark place between 15 to 30 °C. Keep all medicines out of the children's reach.

PRESENTATION: ADVANCE capsules are available in packing containing 10 capsules. ADVANCE liquid is available in a bottle containing 60ml approx.

عمومی خوراک: ڈاکٹر کی ہدایت کے مطابق۔

احتیاط: دوا صرف مستند ڈاکٹر کے زیرِ ہدایت استعمال کریں۔ روشنی، نمی اور گرمی سے بچائیں۔ 15 سے 30 ڈگری سینٹی گریڈ کے درمیان محفوظ کریں۔ تمام ادویات بچوں کی پہنچ سے دور رکھیں۔

Complete medical information available only for doctors on request.

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