Prozyn *Plus*

(Olanzapine + Fluoxetine)
Capsules

پروزائین پلس

(اولینزاپین + فلوآکسٹین) کیپسولز

COMPOSITION

Prozyn Plus 3mg/25mg Capsule	**Prozyn Plus 6mg/25mg Capsule**	**Prozyn Plus 12mg/25mg Capsule**
Each capsule contains	Each capsule contains	Each capsule contains
Olazapine 3mg	Olazapine ..... 6 mg	Olazapine ..... 12 mg
Fluoxetine as Hydrochoride...25mg	Fluoxetine as Hydrochoride...25mg	Fluoxetine as Hydrochoride...25mg

DESCRIPTION: Prozyn Plus (Olanzapine and Fluoxetine) Capsules combines an atypical antipsychotic and a selective serotonin reuptake inhibitor, Olanzapine and Fluoxetine HCl. Olanzapine belongs to the thienobenzodiazepine class. Fluoxetine HCl is a Selective Serotonin Reuptake Inhibitor (SSRI).

MECHANISM OF ACTION: Although the exact mechanism of Olanzapine and Fluoxetine is unknown, it has been proposed that the activation of 3 monoaminergic neural systems (norepinephrine) is responsible for its enhanced effect. In animal studies, Olanzapine and Fluoxetine HCl combination has been shown to produce synergistic increase in norepinephrine and dopamine release in the prefrontal cortex compared with either component alone, as well as increases in serotonin.

PHARMACODYNAMICS: Olanzapine binds with high affinity to the following receptors: serotonin $5HT_2$ and $5HT_6$, dopamine D_{1-4}, histamine H_1 receptor and adrenergic α_1 receptors. Olanzapine is an antagonist with moderate affinity binding for serotonin $5HT_3$ and muscarinic M_{1-5}. Olanzapine binds weakly to GABA, BZD, and b-adrenergic receptors. Fluoxetine is an inhibitor of the serotonin transporter and is a weak inhibitor of the norepinephrine and dopamine transporters.

PHARMACOKINETICS: Absorption and bioavailability: Olanzapine: It is well absorbed and reaches peak concentration approximately in 6 hours following an oral dose. Food does not affect the rate or extent of Olanzapine absorption. It is metabolized extensively by first pass effect with approximately 40% of the dose metabolized before reaching the systemic circulation. Fluoxetine: Following a single oral 40mg dose, peak plasma concentrations of Fluoxetine from 15 to 55ng/ml are observed 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; which is probably not clinically significant. **Distribution:** The in-vitro binding to human plasma proteins of Olanzapine and Fluoxetine in combination is similar to the binding of the individual components. Olanzapine: It is extensively distributed throughout the body with a volume of distribution of approximately 1000L. It is 93% bound to plasma proteins over the concentration range of 7 to 1100ng/ml, binding primarily to albumin and α_1-acid glycoprotein. Fluoxetine: Over the concentration range from 200 to 1000ng/ml, approximately 94.5% of Fluoxetine is bound in vitro to human serum proteins, including albumin and α-glycoprotein. **Metabolism and Elimination:** Olanzapine and Fluoxetine HCl therapy yielded steady state concentrations of nor-fluoxetine similar to those seen with Fluoxetine in the therapeutic dose range. Olanzapine displays linear pharmacokinetics over the clinical dosing range. Its half-life ranges from 21 to 54 hours.

SPECIFIC POPULATIONS: Geriatric: Based on the individual pharmacokinetic profiles of Olanzapine and Fluoxetine, the pharmacokinetics of Olanzapine and Fluoxetine Capsules may be altered in geriatric patients. Caution should be exercised in dosing the elderly, especially if there are other factors that might additively influence drug metabolism and/or pharmacodynamic sensitivity.
Renal Impairment: The pharmacokinetics of Olanzapine and Fluoxetine HCl has not been studied in patients with renal impairment. However, individual pharmacokinetics of Olanzapine and Fluoxetine do not differ significantly in patients with renal impairment. Olanzapine and Fluoxetine Capsules dosing adjustment based upon renal impairment is not routinely required. **Hepatic Impairment:** Based on the individual pharmacokinetic profiles of Olanzapine and Fluoxetine, the pharmacokinetics of Olanzapine and Fluoxetine Capsules may be altered in patients with hepatic impairment. The lowest starting dose should be considered for patients with hepatic impairment.

INDICATIONS: Depressive Episodes Associated with Bipolar I Disorder: Prozyn Plus (Olanzapine and Fluoxetine) Capsules is indicated for the acute treatment of depressive episodes associated with Bipolar I Disorder in adults.
Treatment Resistant Depression: Prozyn Plus (Olanzapine and Fluoxetine) Capsules is indicated for the acute treatment of Treatment Resistant Depression (Major Depressive Disorder in adults who do not respond to 2 separate trials of different antidepressants of adequate dose and duration in the current episode).

CONTRA-INDICATIONS: Prozyn Plus (Olanzapine and Fluoxetine) Capsules is contra-indicated, if patient is hypersensitive to active substances and any of its excipients.

DOSAGE AND ADMINISTRATION: Depressive Episodes Associated with Bipolar I Disorder: Prozyn Plus (Olanzapine and Fluoxetine) Capsules should be administered once daily in the evening, generally beginning with the 6mg/25mg capsules. While food has no appreciable effect on the absorption of Olanzapine and Fluoxetine Capsules given individually, the effect of food on the absorption of Olanzapine and Fluoxetine Capsules has not been studied. Dosage adjustments, if indicated, can be made according to efficacy and tolerability.

Antidepressant efficacy was demonstrated with **P**rozyn **P**lus (Olanzapine and Fluoxetine) Capsules in a dose range of Olanzapine 6mg to 12mg and Fluoxetine 25mg to 50mg. The safety of doses above 18mg/75mg has not been evaluated in clinical studies. It is generally accepted that Bipolar I Disorder, including the depressive episodes associated with Bipolar I Disorder, is a chronic illness requiring chronic treatment. The physician should periodically re-examine the need for continued pharmacotherapy.

Treatment Resistant Depression: Prozyn Plus (Olanzapine and Fluoxetine) Capsules should be administered once daily in the evening, generally beginning with the 6mg/25mg capsules. While food has no appreciable effect on the absorption of Olanzapine and Fluoxetine given individually, the effect of food on the absorption of Prozyn Plus (Olanzapine and Fluoxetine) Capsules has not been studied. Dosage adjustments, if indicated, can be made according to efficacy and tolerability. Antidepressant efficacy was demonstrated with Prozyn Plus (Olanzapine and Fluoxetine) Capsules in a dose range of Olanzapine 6mg to 18mg and Fluoxetine 25mg to 50mg. The safety of doses above 18mg/75mg has not been evaluated in clinical studies. It is generally accepted that Treatment Resistant Depression (Major Depressive Disorder in adult patients who do not respond to 2 separate trials of different antidepressants of adequate dose and duration in the current episode) is a chronic illness requiring chronic treatment. The physician should periodically re-examine the need for continued pharmacotherapy.

Use In Specific Populations: The starting dose of Prozyn Plus (Olanzapine and Fluoxetine) Capsules 3mg/25mg to 6mg/25mg should be used for patients with a predisposition to reactions, patients with hepatic impairment, or patients who exhibit a combination of factors that may slow the metabolism of Prozyn Plus (Olanzapine and Fluoxetine) Capsules (female gender, geriatric age, nonsmoking status) or those patients who may be pharmacodynamically sensitive to Olanzapine. Dosing modification may be necessary in patients who exhibit a combination of factors that may slow metabolism. When indicated, dose escalation should be performed with caution in these patients. Prozyn Plus (Olanzapine and Fluoxetine) Capsules has not been systematically studied in patients >65 years of age or in patients <18 years of age.

Pregnancy Category C: Olanzapine and Fluoxetine HCl should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus, taking into account the risk of untreated Bipolar I Depression or Treatment Resistant Depression.

SIDE EFFECTS: Commonly Observed Adverse Reactions in Short-Term Controlled Studies Including Depressive Episodes Associated with Bipolar I Disorder and Treatment Resistant Depression: **Sexual Dysfunction:** In the pool of controlled Olanzapine and Fluoxetine HCl studies in patients with Bipolar depression, there were higher rates of the treatment-emergent adverse reactions decreased and abnormal in the Olanzapine and Fluoxetine HCl group than in the placebo group. Sexual dysfunction, including priapism has been reported with all SSRIs.

Body as a Whole: Frequent: chills, neck rigidity, photosensitivity reaction; Rare: death.
Cardiovascular System: Frequent: vasodilatation; Infrequent: QT-interval prolonged.
Digestive System: Frequent: diarrhea; Infrequent: nausea and vomiting; Rare: gastrointestinal hemorrhage, liver fatty deposits.
Nervous System: Infrequent: buccoglossal syndrome, coma, depersonalization, emotional hypokinesia, movement disorder; Rare: hyperkinesia, libido increased, withdrawal syndrome.

DRUG INTERACTIONS: Mono Amine Oxidase Inhibitors (MAOI): Olanzapine and Fluoxetine HCl should not be used in combination with MAOI or within a minimum of 14 days of discontinuing therapy with MAOI. There have been reports of serious, sometimes fatal reactions (including rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, and mental status changes that include extreme agitation progressing to delerium and coma) in patients receiving Fluoxetine in combination with an MAOI, and in patients who have recently discontinued Fluoxetine and are then started on MAOI. **CNS Acting Drugs:** Caution is advised if the concomitant administration of Olanzapine and Fluoxetine HCl and other CNS active drugs is required. In evaluating individual cases, consideration should be given to use lower initial doses of the concomitantly administered drugs, using conservative titration schedules, and monitoring of clinical status.

OVERDOSE MANAGEMENT: No specific antidote for either Fluoxetine or Olanzapine overdose is known. Treatment should be supportive and symptomatic.

PRECAUTIONS: Clinical Worsening and Suicide Risk: Patients with Major Depressive Disorder (MDD), both adult and pediatric, may experience worsening of their depression and/or the emergence of suicidal ideation and behavior (suicidality) or unusual changes in behavior, whether or not they are taking medications and this risk may persist until significant remission occurs. Suicide is a known risk of depression and certain other psychiatric disorders; and these disorders themselves are the strongest predictors of suicide. **Neuroleptic Malignant Syndrome (NMS):** A potentially fatal symptom complex sometimes referred to as NMS has been reported in association with administration of drugs, including Olanzapine.

STORAGE
Store below 30°C in a dry place, protect from light. To be dispensed on the prescription of a registered medical practitioner only. Keep out of the reach of children.

PRESENTATION
Prozyn Plus 3mg/25mg capsules are available in 2x7 's blister in a carton.
Prozyn Plus 6mg/25mg capsules are available in 2x7 's blister in a carton.
Prozyn Plus12mg/25mg capsules are available in 2x7 's blister in a carton.

ہدایات :

خوراک: ڈاکٹر کی ہدایت کے مطابق استعمال کریں۔
دوا کو ۳۰ ڈگری سینٹی گریڈ سے کم درجہ حرارت پر خشک جگہ پر رکھیں،
روشنی سے بچائیں۔ صرف رجسٹرڈ ڈاکٹر کے نسخے پر فروخت کریں۔
بچوں کی پہنچ سے دور رکھیں۔

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