DOLF

3mg / 25mg
6mg / 25mg

(Olanzapine / Fluoxetine)
Capsules U.S.P.

QUALITATIVE AND QUANTITATIVE COMPOSITION
DOLF Capsules 3mg/25mg
Each capsule contains:
Olanzapine U.S.P. 3mg
Fluoxetine HCl U.S.P. eq. to Fluoxetine.....25mg

DOLF Capsules 6mg/25mg
Each capsule contains:
Olanzapine U.S.P. 6mg
Fluoxetine HCl U.S.P. eq. to Fluoxetine.....25mg

WARNINGS: SUICIDAL THOUGHTS AND BEHAVIORS; AND INCREASED MORTALITY IN ELDERLYPATIENTS WITH DEMENTIA-RELATED PSYCHOSIS

Suicidal Thoughts and Behaviors - antidepressants increased the risk of suicidal thoughts and behavior in children, adolescents, and young adults in short-term studies. These studies did not show an increase in the risk of suicidal thoughts and behavior with antidepressant use in patients over age 24; there was a reduction in risk with antidepressant use in patients aged 65 and older. In patients of all ages who are started on antidepressant therapy, monitor closely for worsening and emergence of suicidal thoughts and behaviors. Advise families and caregivers of the need for close observation and communication with the prescriber. DOLF is not approved for use in children less than 10 years of age.

Increased Mortality in Elderly Patients with Dementia-Related Psychosis - Elderly patients with dementia related psychosis treated with antipsychotic drugs are at an increased risk of death. DOLF (olanzapine and fluoxetine) is not approved for the treatment of patients with dementia-related psychosis.

DESCRIPTION
DOLF olanzapine and fluoxetine HCl capsules combines an atypical antipsychotic and a selective serotonin reuptake inhibitor, olanzapine).

CLINICAL PHARMACOLOGY
Pharmacodynamics: Mechanism of Action: Although the exact mechanism of DOLF is unknown, it has been proposed that the activation of 3 monoaminergic neural systems (serotonin, norepinephrine, and dopamine) is responsible for its enhanced antidepressant effect.

Pharmacokinetics: Absorption: Following a single oral 12 mg/50 mg dose of DOLF, peak plasma concentration. Olanzapine Olanzapine is well absorbed and reaches peak concentration approximately 6 hours following an oral dose. Food does not affect the rate or extent of olanzapine absorption. Fluoxetine - Following a single oral 40 mg dose, peak plasma concentrations of fluoxetine from 15 to 55 ng/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. DOLF - The in vitro binding to human plasma proteins of olanzapine and fluoxetine in combination is similar to the binding of the individual components. Olanzapine - Olanzapine is extensively distributed throughout the body, with a volume of distribution of approximately 1000 L. Fluoxetine - 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 α1-glycoprotein. **Metabolism & Elimination:** DOLF therapy yielded steady-state concentrations of norfluoxetine similar to those seen with fluoxetine in the therapeutic dose range. Olanzapine - Olanzapine displays line-ar pharmacokinetics over the clinical dosing range. Its half-life ranges from 21 to 54 hours (5th to 95th per-centile; mean of 30 hr), and apparent plasma clearance ranges from 12 to 47 L/hr (5th to 95th percentile; mean of 25 L/hr). Plasma concentrations, half-life, and clearance of olanzapine may vary between individu-als on the basis of smoking status, gender, and age. Approximately 57% and 30% of the dose was recovered in the urine and feces, respectively. Fluoxetine-Fluoxetine is extensively metabolized in the liver to its only identified active metabolite, norfluoxetine, via the CYP2D6 pathway. A number of unidentified metabolites exist. The primary route of elimination appears to be hepatic metabolism to inactive metabolites excreted by the kidney.

INDICATIONS AND USAGE
DOLF is indicated for the treatment of:
• Acute depressive episodes in Bipolar I Disorder
• Treatment resistant depression (Major Depressive Disorder in patient who do not respond to 2 separate trials of different antidepressants of adequate dose and duration in the current episode).

CONTRAINDICATIONS
• Monoamine Oxidase Inhibitors (MAOIs): The use of MAOIs intended to treat psychiatric disorders with DOLF or within 5 weeks of stopping treatment with DOLF is contraindicated because of an increased risk of serotonin syndrome.
• Pimozide and thioridazine prolong the QT interval. DOLF can increase the levels of pimozide and thioridazine through inhibition of CYP2D6. DOLF can also prolong the QT interval.

INTERACTIONS
The risks of using DOLF in combination with other drugs have not been extensively evaluated in systematic studies. The drug-drug interactions sections of fluoxetine and olanzapine are applicable to DOLF. As with all drugs, the potential for interaction by a variety of mechanisms (e.g., pharmaco-dynamic, pharmacokinetic drug inhibition or enhancement, etc.) is a possibility. **CNS Acting Drugs:** Caution is advised if the concomitant administration of DOLF and other CNS-active drugs is required. In evaluating individual cases, consideration should be given to using lower initial doses of the concomitantly administered drugs, using conservative titration schedules, and monitoring of clinical status. **Serotonergic Drugs:** The concomitant use of DOLF with MAOIs intended to treat psychiatric disorders is contraindicated. DOLF should also not be started in a patient who is being treated with MAOIs such as linezolid or intravenous methylene blue.
• Drugs Metabolized by CYP2D6: Fluoxetine is a potent inhibitor of CYP2D6 enzyme pathway
• Tricyclic Antidepressants (TCAs): Monitor TCA levels during coadministration with DOLF or when DOLF has been recently discontinued.
• CNS Acting Drugs: Caution is advised if the concomitant administration of DOLF and other CNS-active drugs is required
• Antihypertensive Agent: Enhanced antihypertensive effect
• Levodopa and Dopamine Agonists: May antagonize levodopa/dopamine agonists
• Benzodiazepines: May potentiate orthostatic hypotension and sedation
• Clozapine: May elevate clozapine levels
• Haloperidol: Elevated haloperidol levels have been observed
• Carbamazepine: Potential for elevated carbamazepine levels and clinical anticonvulsant toxicity
• Phenytoin: Potential for elevated phenytoin levels and clinical anticonvulsant toxicity
• Alcohol: May potentiate sedation and orthostatic hypotension
• Fluvoxamine: May increase olanzapine levels; a lower dose of the olanzapine component of DOLF should be considered
• Drugs that Interfere with Hemostasis: (e.g., NSAIDs, Aspirin, Warfarin, etc.): May potentiate the risk of bleeding
• Drugs Tightly Bound to Plasma Proteins: Fluoxetine may cause shift in plasma concentrations

USE IN SPECIFIC POPULATION
Pregnancy: DOLF should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. **Nursing mothers:** It is recommended that women not breast-feed when receiving DOLF. **Pediatric Use:** Safety and efficacy of DOLF for the treatment of bipolar I depression in patients under 10 years of age have not been established. Safety and efficacy of DOLF for treatment resistant depression in patients under 18 years of age have not been established. **Geriatric use:** Caution should be used in dosing the elderly, especially if there are other factors that might additively influence drug metabolism and/or pharmacodynamic sensitivity. **Hepatic Patients:** Use a lower or less frequent dose in patients with cirrhosis.

PRECAUTIONS
Suicidal Thoughts and Behaviors in Children, Adolescents, and Young Adults: All patients being treated with antidepressants for any indication should be monitored appropriately and observed closely for clinical worsening, suicidality, and unusual changes in behavior, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases.

Increased Mortality in Elderly Patients with Dementia Related Psychosis: Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. DOLF is not approved for the treatment of patients with dementia-related psychosis.

Neuroleptic Malignant Syndrome (NMS): If after recovering from NMS, a patient requires treatment with an antipsychotic, the patient should be carefully monitored, since recurrences of NMS have been reported. **Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS):** Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) has been reported with olanzapine exposure. DRESS may present with a cutaneous reaction (such as rash or exfoliative dermatitis), eosinophilia, fever, and/or lymphadenopathy with systemic complications such as hepatitis, nephritis, pneumonitis, myocarditis, and/or pericarditis. DRESS is sometimes fatal. Discontinue DOLF if DRESS is suspected. **Metabolic Changes:** Atypical antipsychotic drugs have been associated with metabolic changes including hyperglycemia, dyslipidemia, and weight gain. Metabolic changes may be associated with increased cardiovascular/cerebrovascular risk. **Hyperglycemia and Diabetes Mellitus:** Physicians should consider the risks and benefits when prescribing DOLF to patients with an established diagnosis of diabetes mellitus, or having borderline increased blood glucose level (fasting 100-126 mg/dL, non-fasting 140-200 mg/dL). Patients taking DOLF should be monitored regularly for worsening of glucose control. **Long Elimination Half-Life of Fluoxetine:** Because of the long elimination half-lives of fluoxetine and its major active metabolite, changes in dose will not be fully reflected in plasma for several weeks, affecting both strategies for titration to final dose and withdrawal from treatment. **Discontinuation Adverse Reactions:** Plasma fluoxetine and norfluoxetine concentration decrease gradually at the conclusion of therapy, which may minimize the risk of discontinuation symptoms with this drug.

ADVERSE REACTIONS
The following adverse reactions are discussed in more detail in other sections of the labeling: Suicidal Thoughts and Behaviors in Children, Adolescents, and Young Adults, increased Mortality in Elderly Patients with Dementia-Related Psychosis, Neuroleptic Malignant syndrome (NMS), Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS), Hyperglycemia, Dyslipidemia, Weight Gain, Serotonin Syndrome, Angle-Closure Glaucoma, Allergic Reactions and Rash, Activation of Mania/Hypomania, Tardive Dyskinesia, Orthostatic Hypotension, Falls, Leukopenia, Neutropenia, and Agranulocytosis, Dysphagia, Seizures, Abnormal Bleeding, Hyponatremia, Potential for Cognitive and Motor Impairment, Body Temperature Dysregulation, QT Prolongation, Hyperprolactinemia, Discontinuation Adverse Reactions.

DRUG ABUSE AND DEPENDENCE
Physicians should carefully evaluate patients for history of drug abuse and follow such patients closely, observing them for signs of misuse or abuse of DOLF (e.g., development of tolerance, incrementation of dose, drug-seeking behavior).

DOSAGE AND ADMINISTRATION
-Depressive Episodes Associated with Bipolar I Disorder Adults - Administer DOLF once daily in the evening, generally beginning with the 6mg/25mg (mg olanzapine/mg equivalent fluoxetine) capsule. While food has no appreciable effect on the absorption of olanzapine and fluoxetine given individually, the effect of food on the absorption of DOLF has not been studied. Make dosage adjustments, if indicated, according to efficacy and tolerability. Children and Adolescents (10 to 17 years of age) - Administer DOLF once daily in the evening, generally beginning with the 3mg/25mg capsule, without regard to meals, with a recommended target dose within the approved dosing range (6/25; 6/50; 12/25; 12/50 mg). **Treatment Resistant Depression:** Administer DOLF once daily in the evening, generally beginning with the 6 mg/25 mg capsule. The safety of doses above 18 mg/75 mg has not been evaluated in clinical studies. Periodically reexamine the need for continued pharmacotherapy. **Specific Populations:** Start DOLF at 3 mg/25 mg or 6 mg/25 mg in patients with a predisposition to hypotensive reactions, patients with hepatic impairment, or patients who exhibit a combination of fac-tors that may slow the metabolism of DOLF (female gender, geriatric age, nonsmoking status) or those patients who may be pharmacodynamically sensitive to olanzapine. Titrate slowly and adjust dosage as needed in patients who exhibit a combination of factors that may slow metabolism. DOLF has not been systematically studied in patients >65 years of age or in pa-tients.
-Switching a Patient to or From a Monoamine Oxidase Inhibitor (MAOI) Intended to Treat **Psychiatric Disorders:** At least 14 days should elapse between discontinuation of an MAOI intended to treat psychiatric disorders and initiation of therapy with DOLF. Conversely, at least 5 weeks should be allowed after stopping DOLF before starting an MAOI intended to treat psychiatric disorders

OVERDOSAGE:
In managing overdose, consider the possibility of multiple drug involvement. In case of acute overdose, establish and maintain an airway and ensure adequate ventilation, which may include intubation. Induction of emesis is not recommended as the possibility of obtundation, seizures, or dystonic reactions of the head and neck following overdose may create a risk for aspiration. Commence cardiovascular monitoring immediately and include continuous electrocardiographic monitoring to detect possible arrhythmias. A specific precaution involves patients who are taking or have recently taken DOLF and may have ingested excessive quantities of a TCA (tricyclic antidepressant). In such cases, accumulation of the parent TCA and/or an active metabolite increases the possibility of serious sequelae and extends the time needed for close medical observation. Due to the large volume of distribution of olanzapine and fluoxetine, forced diuresis, dialysis, hemoperfusion, and exchange transfusion are unlikely to be of benefit. No specific anti-dote for either fluoxetine or olanzapine overdose is known. Treat hypotension and circulatory collapse with appropriate measures such as intravenous fluids and/or sympathomimetic agents. Do not use epinephrine, dopamine, or other sympathomimetic with β-agonist activity, since beta stimulation may worsen hypoten-sion in the setting of olanzapine-induced alpha blockade.

INSTRUCTIONS
Store at 20°C to 25°C, excursions permitted to 15°C - 30°C. Protect from sunlight and moisture. Keep all medicines out of the reach of children.

PRESENTATION
DOLF(Olanzapine/Fluoxetine) Capsules 3mg/25mg are available in Alu-Alu blister pack of 3x10's with leaflet.
DOLF(Olanzapine/Fluoxetine) Capsules 6mg/25mg are available in Alu-Alu blister pack of 3x10's with leaflet.

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