OXEZAC

Capsules

Composition
Each Capsule contains Fluoxetine (as HCl) Equivalent to 20 mg Fluoxetine.

Action
Fluoxetine is an antidepressant intended for oral administration. Fluoxetine is a selective inhibitor of serotonin reuptake, its presumed mechanism of action. Fluoxetine has practically no affinity to other receptors such as α_1-, α_2- and β-adrenergic; serotonergic; dopaminergic; histaminergic; muscarinic; and GABA receptors.

Pharmacokinetics

Absorption and Distribution

Fluoxetine is well absorbed after oral administration. Peak plasma concentration is reached in six to eight hours. Fluoxetine is extensively bound to plasma proteins. Fluoxetine is widely distributed. Steady-state plasma concentrations are achieved after dosing for several weeks. Steady-state concentrations after prolonged dosing are similar to concentrations seen at four to five weeks.

Metabolism and Excretion

Fluoxetine is extensively metabolised in the liver to norfluoxetine and a number of other, unidentified metabolites which are excreted in urine. The elimination half-life of Fluoxetine is four to six days and that of its active metabolite is four to 16 days.

Pharmacological Properties

Pharmacodynamic properties - the etiology of premenstrual dysphoric disorder is unknown, but endogenous steroids (neuro and/or ovarian) involved in the menstrual cycle may interrelate with neuronal serotonergic activity.

Clinical data premenstrual dysphoric disorder (PMDD): In clinical trials fluoxetine was shown to be effective in relieving both the cyclical mood changes and physical symptoms (tension, irritability and dysphoria, bloating and breast tenderness) associated with PMDD.

Indications
- Depression and its associated anxiety.
- Bulimia nervosa.
- Obsessive-Compulsive disorder.
- Premenstrual dysphoric disorder - a severe form of PMS.

Diagnosis of PMDD: The essential features of PMDD are clear and established cyclicity of symptoms (occurring during the last week of the luteal phase in most menstrual cycles) such as depressed mood, anxiety, affective lability, and physical symptoms such as breast tenderness or swelling, headaches, joint or muscle pain, bloating, and weight gain. PMDD is a severe clinical entity and is distinguished from the broader premenstrual syndrome by the intensity of its symptoms (particularly mood symptoms) and the extent to which it interferes with social and/or occupational function.

Contraindications
Hypersensitivity

Fluoxetine is contraindicated in patients known to be hypersensitive to Fluoxetine.

MAOIs

Fluoxetine should not be used in combination with a monoamine oxidase inhibitor (MAOI) or within a minimum of 14 days of discontinuing treatment with a MAOI. At least five weeks should elapse between discontinuation of Fluoxetine and initiation of therapy with a MAOI. If Fluoxetine has been prescribed chronically and/or at a high dose, a longer interval should be considered. Serious and fatal cases of serotonin syndrome (which may resemble and be diagnosed as neuroleptic malignant

syndrome) have been reported in patients treated with Fluoxetine and a MAOI in close temporal proximity.

Warnings

Clinical Worsening and Suicide Risk

The risk of suicide attempt is inherent in depression and other psychiatric disorders and may persist until significant remission occurs. As with other drugs with similar pharmacological action (antidepressants), isolated cases of suicidal ideation and suicidal behaviors have been reported during Fluoxetine therapy or early after treatment discontinuation. This risk must be considered in all depressed patients.

Although a causal role for Fluoxetine in inducing such events has not yet been established, some analyses from pooled studies of antidepressants in psychiatric disorders found an increased risk for suicidal ideation and/or suicidal behaviors in paediatric and young adult (<25 years of age) patients compared to placebo. Patients with depression may experience worsening of their depressive symptoms and/or the emergence of suicidal ideation and whether or not they are taking antidepressant medications, and this risk may persist until significant remission occurs. As improvement may not occur during the first few weeks or more of treatment, patients should be closely monitored for clinical worsening and suicidality, especially at the beginning of a course of treatment, or at the time of dose changes, either increases or decreases. Consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medication, in patients whose depression is persistently worse or whose emergent suicidality is severe, abrupt in onset, or was not part of the patient's presenting symptoms. Patients (and caregivers of patients) should be alerted about the need to closely monitor for any worsening of their condition and/or the emergence of suicidal ideation/behavior or thoughts of harming themselves and to seek medical advice immediately if these symptoms present. Physicians should encourage patients of all ages to report any distressing thoughts or feelings at any time. Patients with co-morbid depression associated with other psychiatric disorders being treated with antidepressants should be similarly observed for clinical worsening and suicidality.

Pooled analyses of 24 short-term (4 to 16 weeks), placebo-controlled trials of nine antidepressant medicines [selective serotonin reuptake inhibitors (SSRIs) and others] in 4400 children and adolescents with major depressive disorder, obsessive compulsive disorder, or other psychiatric disorders have revealed a greater risk of adverse events representing suicidal behavior or thinking (suicidality) during the first few months of treatment in those receiving antidepressants. The average risk of such events in patients treated with an antidepressant was 4%, compared with 2% of patients given placebo. There was considerable variation in risk among the antidepressants, but there was a tendency towards an increase for almost all antidepressants studied. The risk of suicidality was most consistently observed in the major depressive disorder trials, but there were signals of risk arising from trials in other psychiatric indications (obsessive compulsive disorder and social anxiety disorder) as well. No suicides occurred in these trials. It is unknown whether the suicidality risk in children and adolescent patients extends to use beyond several months. The nine antidepressant medicines in the pooled analyses included five SSRIs (citalopram, Fluoxetine, fluvoxamine, paroxetine, and sertraline) and four non-SSRIs (bupropion, mirtazapine, nefazodone, venlafaxine).

Symptoms of anxiety, agitation, panic attacks, insomnia, irritability, hostility (aggressiveness), impulsivity, akathisia (psychomotor restlessness), hypomania, and mania, have been reported in adults, adolescents and children being treated with antidepressants for major depressive disorder as well as for other indications, both psychiatric and non-psychiatric. Although a causal link between the emergence of such symptoms and either worsening of depression and/or emergence of suicidal impulses has not been established, there is concern that such symptoms may be precursors of emerging suicidality.

Families and caregivers of children and adolescents being treated with antidepressants for major depressive disorder or for any other condition (psychiatric or nonpsychiatric) should be informed about the need to monitor these patients for the emergence of agitation, irritability, unusual changes

in behavior, and other symptoms described above, as well as the emergence of suicidality, and to report such symptoms to health care providers immediately. It is particularly important that monitoring be undertaken during the initial few months of antidepressant treatment or at times of dose increase or decrease.

Prescriptions for Fluoxetine should be written for the smallest quantity of medicine consistent with good patient management, in order to reduce the risk of overdose.

Mania and Bipolar Disorder
A major depressive episode may be the initial presentation of bipolar disorder. It is generally believed (though not established in controlled trials) that treating such an episode with any antidepressant alone may increase the likelihood of a mixed/manic episode in patients at risk for bipolar disorder. Prior to initiating treatment with an antidepressant, patients with depressive symptoms should be adequately screened to determine if they are at risk for bipolar disorder. It should be noted that Fluoxetine is not approved for use in treating bipolar depression.

Rash
Rash, anaphylactoid events, and progressive systemic events, sometimes serious and involving skin, kidney, liver or lungs have been reported in patients taking Fluoxetine. Upon the appearance of rash, or of other possible allergic phenomena for which an alternative etiology cannot be identified Fluoxetine should be discontinued.

Adverse Reactions

In clinical trials

Body system/Undesirable Effects	***Incidence %***
Body as a Whole	
Anaphylactoid reaction	0.02
Asthenia	17.9
Chills	2.2
Dry Mouth	8.6
Photosensitivity	0.05
Pruritis	3.5
Rash	4.8
Serum sickness-like reaction	0.02
Sweating	9.9
Urticaria	1.6
Vasculitis	0.02
Vasodilatation	2.9
Digestive System	
Diarrhoea	14.1
Dyspepsia	8.7
Dysphagia	0.9
Nausea	22.4
Taste Perversion	1.6
Vomiting	3.3
Hemic and Lymphatic System	

Body system/Undesirable Effects	***Incidence %***
Ecchymosis	0.6
Nervous System	
Abnormal dreams	2.1
Anorexia	9.9
Anxiety	12.9
Ataxia	0.2
Buccoglossal syndrome	0.25
Concentration impaired/Thought process Impaired	4.5
Depersonalization	0.6
Dizziness	10.3
Insomnia	20.2
Manic reaction	0.11
Myoclonus	0.3
Nervousness	14.8
Psychomotor restlessness	0.2
Somnolence	15.2
Tremor	11.1
Twitching	0.9
Palpitation	2.3
Weight Loss	1.6
Respiratory	
Yawn	4.4
Skin and Appendages	
Alopecia	0.4
Special Senses	
Blurred vision	2.1
Mydriasis	0.45
Urogenital System	
Anorgasmia	0.2
Delayed or absent ejaculation	2.0
Impotence	2.9
Libido decreased	4.4
Priapism/Prolonged erection*	0.1
Urinary frequency	1.8
Urination impaired	0.41

Post-Marketing Experience

The following events have not been reported in clinical trials of Fluoxetine, but have been reported in clinical practice and are associated with Fluoxetine therapy. These events are classified as either very rare (occurring in less than 1/10000 patients) or uncommon (occurring in 1/100 to 1/1000 patients).

Body as a Whole: (Very rare) angioedema; serotonin syndrome, erythema multiforme.

Digestive System: (Very rare) idiosyncratic hepatitis.

Endocrine System: (Very rare) inappropriate secretion of antidiuretic hormone.

Blood and Lymphatic System: (Rare) haemorrhagic manifestations (e.g. gynecological hemorrhages, gastrointestinal bleedings and other cutaneous or mucous bleedings).

Nervous System: (Uncommon) seizures.

Special Populations: Children: (Very rare) headache

Precautions

Seizures
As with other antidepressants, Fluoxetine should be introduced cautiously in patients who have a history of seizures.

Hyponatremia
Cases of hyponatremia (some with serum sodium lower than 110 mmol/L) have been reported. The majority of these cases occurred in elderly patients and in patients treated with diuretics or otherwise volume-depleted.

Glycemic Control
In patients with diabetes, hypoglycemia has occurred during therapy with Fluoxetine and hyperglycemia has developed following discontinuation. Insulin and/or oral hypoglycemic dosage may need to be adjusted when Fluoxetine therapy is initiated or discontinued.

Withdrawal Reactions
Discontinuation symptoms have been reported in association with selective serotonin reuptake inhibitors (SSRIs). Because of the long elimination half-life of Fluoxetine, and its active metabolite norfluoxetine, plasma Fluoxetine and norfluoxetine concentrations decrease gradually at the conclusion of therapy, which reduces greatly the likelihood of developing discontinuation symptoms and makes dosage tapering unnecessary in most patients. Common symptoms associated with withdrawal of SSRIs include dizziness, paraesthesia, headache, anxiety and nausea. Onset of symptoms can occur within a day of discontinuation but may be delayed, particularly in the case of Fluoxetine, due to its long half-life. The majority of symptoms experienced on withdrawal of SSRIs are non serious, self-limiting and have varying durations. Fluoxetine has been only rarely associated with such symptoms.

Hemorrhage
There have been reports of cutaneous bleeding abnormalities such as ecchymosis and purpura with SSRI's. Ecchymosis has been reported as an infrequent event during treatment with Fluoxetine. Other haemorrhagic manifestations (e.g., gynecological hemorrhages, gastrointestinal bleedings and other cutaneous or mucous bleedings) have been reported rarely. Caution is advised in patients with a history of bleeding disorders as well as in patients taking SSRI's particularly in concomitant use with oral anticoagulants, drugs known to affect platelet function (e.g. atypical antipsychotics such as clozapine, phenothiazines, most TCA's, aspirin, NSAID's) or other drugs that may increase risk of bleeding.

Pregnancy
Category D

There is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.

Nursing Mothers
Fluoxetine is excreted in human milk; therefore, caution should be exercised when Fluoxetine is administered to nursing women.

Effects on Ability to Drive and Use Machines
Psychoactive medicines may impair judgment, thinking, or motor skills. Patients should be advised to avoid driving a car or operating machinery until they are reasonably certain that their performance is not affected.

Information for Patients and Families
Physicians are advised to discuss the following issues with patients for whom they prescribe Fluoxetine:

- Because fluoxetine may impair judgment, thinking, or motor 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.
- Patients should be advised to inform their physician if they are taking or plan to take any prescription or over-the-counter medicines, or alcohol.
- Patients should be advised to inform their physician if they become pregnant or intend to become pregnant during therapy.
- Patients should be advised to notify their physician if they are breast feeding an infant.
- Patients should be advised to notify their physician if they develop a rash or hives.

Drug Interactions

Monoamine Oxidase Inhibitors
See Contraindications.

Medicines Metabolised by Cytochrome P450IID6 Isoenzyme
Because Fluoxetine has the potential to inhibit the cytochrome P450IID6 isoenzyme, therapy with medications that are predominantly metabolised by the P450IID6 system and that have a relatively narrow therapeutic index should be initiated at the low end of the dose range if a patient is receiving Fluoxetine concurrently or has taken it in the previous five weeks. If Fluoxetine is added to the treatment range of a patient already receiving such a medicine, the need for decreased dose of the original medication should be considered.

CNS Active Medicines
Changes in the blood levels of phenytoin, carbamazepine, haloperidol, clozapine, diazepam, alprazolam, lithium, imipramine and desipramine, and in some cases, clinical manifestations of toxicity have been observed. Consideration should be given to using conservative titration schedules of the concomitant medicine and monitoring of clinical status. Concomitant use of other drugs with serotonergic activity (e.g. SNRIs, SSRIs, triptans or tramadol) may result in serotonin syndrome.

Protein Binding
Because Fluoxetine is tightly bound to plasma protein, the administration of Fluoxetine to a patient taking another medicine that is tightly bound to protein may cause a shift in plasma concentrations of either medicine.

Drugs that interfere with hemostasis
Caution is advised in patients with a history of bleeding disorders as well as in patients taking SSRI's, particularly in concomitant use with oral anticoagulants, medicines known to affect platelet function (e.g. atypical antipsychotics such as clozapine, phenothiazines, most TCA's, aspirin, NSAID's) or other drugs that may increase risk of bleeding.

Warfarin
Altered anti-coagulant effects (laboratory values and/or clinical signs and symptoms), with no consistent pattern, but increased bleeding, have been reported uncommonly when Fluoxetine is co-administered with warfarin. As is prudent in concomitant use of warfarin with many other medicines, patients receiving warfarin therapy should receive careful monitoring when Fluoxetine is initiated or stopped.

Electroconvulsive Therapy (ECT)
There have been rare reports of prolonged seizures in patients on Fluoxetine receiving ECT treatment.

Elimination Half-Life
The long elimination half-lives of Fluoxetine and its principal metabolite, norfluoxetine, are of potential consequence when medicines are prescribed which might interact with either substance following the discontinuation of Fluoxetine.

Dosage and Administration

Dosage

Depression
20 mg per day is the recommended initial dose.

Bulimia Nervosa
60 mg per day is the recommended dose.

Obsessive-Compulsive Disorder
20 mg to 60 mg per day is the recommended dose.

Premenstrual Dysphoric Disorder
20 mg per day is recommended continuously throughout the menstrual cycle. Initial treatment should be limited to six months, after which patients should be reassessed regarding the benefit of continued therapy.

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

Administration

Administration with Food
OXEZAC may be administered with or without food.

Age
There are no data to suggest that alternate dosing is required on the basis of age alone.

Use in Children and Adolescents (under 18 years of age)
The safety and efficacy of Fluoxetine for the treatment of children and adolescents less than 18 years of age has not been established.

Concurrent Disease and/or Concomitant Medication
A lower or less frequent dose should be considered in patients with hepatic impairment, with concurrent diseases, or who are taking multiple medications.

Over dosage

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 to cardiac arrest, pulmonary dysfunction, and signs of altered CNS status ranging from excitation to coma. Fatality attributed to overdose of Fluoxetine alone has been extremely rare.

Management
Cardiac and vital signs monitoring is recommended, along with general symptomatic and supportive measures. No specific antidote is known. Forced diuresis, dialysis, hemoperfusion, and exchange transfusion are unlikely to be of benefit. In managing Overdosage, consider the possibility of multiple medicine involvement.

Presentation
Box of 30 capsules