FLUOXETINE-TEVA 20 MG CAPSULES

Composition
Each capsule contains: Active Ingredient
Fluoxetine (as hydrochloride) 20 mg
Other Ingredients:
Simethicone emulsion, colloidal silicon dioxide, pregelatinized starch.

Mechanism of Action
Fluoxetine is an antidepressant which is chemically unrelated to tetracyclic or other available antidepressant agents. The mechanism of action of fluoxetine is complex and in some ways resembles that of other antidepressant agents, particularly those agents (e.g., clomipramine, trazodone) that predominantly potentiate the pharmacologic effects of serotonin. Unlike other currently available serotonin-enhancing antidepressant agents, fluoxetine is a highly selective reuptake inhibitor of serotonin and has little or no effect on other neurotransmitters.

Pharmacodynamics
Central Nervous System Effects
The precise mechanism of antidepressant action of fluoxetine is unclear, but the drug has been shown to selectively inhibit the reuptake of serotonin (5-HT) at the presynaptic neuronal membrane. Fluoxetine- induced inhibition of serotonin reuptake causes increased synaptic concentrations of serotonin in the CNS, resulting in numerous functional changes associated with enhanced serotonergic neurotransmission. Unlike most other current available antidepressant agents, fluoxetine appears to have minimal or no effect on the reuptake of norepinephrine or dopamine and does not exhibit clinically important anticholinergic, antihistaminic, or (alpha)1- adrenergic blocking activity at usual therapeutic dosages.

Cardiovascular Effects
The cardiovascular effects of fluoxetine have been studied in animals and to a limited extent in humans. Unlike most other antidepressant agents (e.g., tricyclic antidepressants, MAO inhibitors), fluoxetine has been associated with only minimal cardiovascular effects. The absence of substantial activity, (alpha)1-adrenergic blocking activity, catecholamine-potentiating effects, and quinidine-like cardiotoxic effects appears to be the principal reason for the general lack of cardiovascular effects associated with fluoxetine.
Fluoxetine generally does not appear to affect cardiac conduction, and clinically important ECG changes have not been reported in patients without preexisting heart disease receiving therapeutic dosages of the drug. Unlike tricyclic antidepressants, which commonly cause an increase in heart rate, fluoxetine has been reported to reduce heart rate by an average of about 3 beats/minute in patients receiving usual therapeutic dosages of the antidepressant.

Effects on Appetite and Body Weight
Like some other serotonergic agents (e.g., fenfluramine), fluoxetine possesses anorectic activity. Although the precise mechanism has not been clearly established, results of animal studies indicate that the drug's appetite-inhibiting action may result from serotonin- reuptake blockade and the resultant increase in serotonin availability at the neuronal synapse.

Effects on Alcohol Intake
Like some other serotonergic agents, fluoxetine produces a dose-dependent decrease in voluntary alcohol intake in normal and alcohol-preferring animals. Fluoxetine has been shown to reduce alcohol consumption in a limited number of heavy drinkers receiving 60 mg of the drug daily. Because serotonin appears to be involved in the regulation of alcohol intake, it has been suggested that fluoxetine may attenuate alcohol consumption via enhanced serotonergic neurotransmission.

Neuroendocrine Effects
Fluoxetine affects the endocrine system. Like other selective inhibitors of serotonin reuptake, the drug has produced a dose-related increase in serum corticosterone concentrations in animals.
Fluoxetine also has increased corticotropin (ACTH) and vasopressin (antidiuretic hormone, ADH) concentrations in peripheral plasma and has increased corticotropin and corticotropin-releasing factor (CRF) concentrations in hypophysial portal blood. These effects may represent the initial step in fluoxetine-induced elevation of plasma corticosterone concentrations.
The effects of fluoxetine on serum prolactin concentrations have not been clearly established. Administration of the drug alone in animals and humans usually does not substantially alter prolactin concentrations. However, administration of fluoxetine alone has been reported to increase serum prolactin concentrations in young but not old male rats in one study. Fluoxetine- induced effects on prolactin secretion appear to be serotonergically mediated.

Other Effects
Fluoxetine has demonstrated some antimyoclonic activity in animals and humans. Although the mechanism of fluoxetine's antimyoclonic activity has not been fully elucidated, some forms of myoclonus appear to be related to impaired serotonergic neurotransmission.

Pharmacokinetics
Absorption
Fluoxetine is well absorbed after oral administration. In man, following a single 40 mg dose, peak plasma concentrations of fluoxetine from 15 to 55 ng/ml were observed after 6 to 8 hours. Food appears to affect the rate but not the extent of absorption.

Distribution
Distribution of fluoxetine and its metabolites into human body tissues and fluids has not been fully characterized. Limited pharmacokinetic data obtained during long-term administration of fluoxetine to animals suggest that the drug and some of its metabolites, including norfluoxetine, are widely distributed in body tissues, with highest concentrations occurring in the lungs and liver. The drug crosses the blood-brain barrier in humans and animals.
At in vitro plasma concentrations of 200-1000 ng/ml, fluoxetine is approximately 94.5% bound to plasma proteins, including albumin and (alpha)1-acid glycoprotein; the extent of protein binding appears to be independent of plasma concentration. The extent of fluoxetine protein binding does not appear to be altered substantially in patients with hepatic cirrhosis or renal impairment, including those undergoing hemodialysis.

Metabolism
Fluoxetine is extensively metabolized in the liver to a major active metabolite, norfluoxetine and other, unidentified metabolites. Norfluoxetine, a desmethyl metabolite, is also a serotonin uptake inhibitor, contributing to the long duration of action of the drug. The complexity of fluoxetine's metabolism has several consequences which may potentially affect its clinical use. The half-life of fluoxetine after a single dose is 1 to 4 days and after multiple dosing 2 to 7 days. The corresponding values for norfluoxetine are similar for single and multiple dosing. After 30 days of dosing at 40 mg/day, plasma concentrations of fluoxetine in the range of 91 to 302 ng/ml and norfluoxetine in the range of 72 to 258 ng/ml have been observed. Plasma concentrations of fluoxetine were higher than those predicted by single dose studies, presumably because fluoxetine's metabolism is not proportional to dose. Norfluoxetine, however, appears to have linear pharmacokinetics.
Steady state plasma levels are attained after 4 to 5 weeks of continuous drug administration.

Patients receiving fluoxetine at doses of 40 to 80 mg/day over periods as long as 3 years, exhibited on average, plasma concentrations similar to those seen among patients treated for 4 to 5 weeks.
As might be predicted from its primary site of metabolism, liver impairment can affect the elimination of fluoxetine. In patients with alcohol-induced cirrhosis, the half-lives of both fluoxetine and norfluoxetine were prolonged and plasma clearance was significantly reduced. This suggests that the use of fluoxetine in patients with liver disease must be approached with caution (see Warnings). In renal disease, in single dose studies, the pharmacokinetics of fluoxetine and norfluoxetine were similar among subjects with all levels of impaired renal function including anephric patients on chronic hemodialysis. While the possibility exists that renally excreted metabolites of fluoxetine may accumulate to higher levels in patients with severe renal dysfunction, use of a lower or less frequent dose is not routinely necessary in renally impaired patients.

Effect of Age Upon the Metabolism of Fluoxetine
The effects of age upon the metabolism of fluoxetine have not been fully explored. The disposition of single doses of fluoxetine in healthy elderly subjects (older than 65 years of age) did not differ significantly from that in younger normal subjects. However, given the long half- life and non-linear disposition of the drug, available data is not adequate to rule out the possibility of altered pharmacokinetics in the elderly, particularly if they have systemic illness or are receiving multiple drugs for concomitant diseases.(see Warnings).

Elimination
Elimination of metabolites occurs primarily in the urine with a smaller amount also being present in the feces.
Because of the long half-lives of fluoxetine and norfluoxetine, it may take up to 1 to 2 months for the active drug substance to disappear from the body. This is of potential consequence in withdrawal of fluoxetine.

Indications
- For the treatment of depression.
  The effectiveness of fluoxetine in long-term use (i.e. for more than 5 to 6 weeks) has not been evaluated in controlled trials. Therefore, the physician who decides to use fluoxetine for long periods should periodically reevaluate the long-term usefulness for the individual patient.
- Fluoxetine is also indicated in the treatment of obsessive-compulsive disorder (OCD). Effectiveness in long-term use, i.e. for more than 13 weeks, has not been established. (see Dosage and Administration).
- Fluoxetine is also indicated for the treatment of binge-eating and vomiting behaviors in bulimia nervosa.

Contraindications
Patients with known hypersensitivity to any ingredient of the preparation.
There have been reports of serious, sometimes fatal, reactions in patients receiving fluoxetine in combination with a monoamine oxidase (MAO) inhibitor, and in patients who have recently discontinued fluoxetine and are then started on an MAO inhibitor. Therefore, fluoxetine should not be used concurrently with a MAO inhibitor.

Transfer from MAO-Inhibitor Therapy to Fluoxetine Therapy.
A lapse of 14 days should be allowed between the discontinuation of a MAO-inhibitor and the institution of fluoxetine.

Transfer from Fluoxetine Therapy to MAO-Inhibitor Therapy.
Since fluoxetine and its major metabolite have very long elimination half-lives, at least 5 weeks should be allowed after discontinuing fluoxetine before starting a MAO inhibitor.

Warnings
Rash and Allergic Events
Approximately 4% of patients treated with fluoxetine during premarketing testing have developed rash and/or urticaria. Among these cases, almost a third were withdrawn from treatment because of the rash and/or systemic signs or symptoms associated with the rash. Upon discontinuation of fluoxetine and the institution of treatment with antihistamines or steroids, recovery has been reported. Anaphylactoid events including bronchospasm, angioedema, and urticaria, alone and in combination, have been reported. Pulmonary events, including inflammatory processes and/or fibrosis,have been reported rarely. Upon the appearance of rash or other possibly allergic phenomena, fluoxetine should be discontinued. Whether these systemic events and rash have a common underlying cause or are due to different etiologies or pathogenic processes is not known. Furthermore, a specific underlying immunologic basis for these events has not been identified. Upon the appearance of rash or of other possibly allergic phenomena for which an alternative etiology cannot be identified, fluoxetine should be discontinued.

Sexual dysfunction
Selective serotonin reuptake inhibitors (SSRIs)/serotonin norepinephrine reuptake inhibitors (SNRIs) may cause symptoms of sexual dysfunction. There have been reports of long-lasting sexual dysfunction where the symptoms have continued despite discontinuation of SSRIs/SNRIs.

Drug Dependence
Although data available to date do not suggest a tendency to drug dependence, it is recommended that physicians should carefully evaluate patients for history of drug abuse and follow such patients closely, observing them for signs of misuse or abuse of fluoxetine.

Mutagenicity
Fluoxetine and norfluoxetine have been shown to have no genotoxic effects.

Carcinogenicity
The dietary administration of fluoxetine to rats and mice for 2 years at doses of up to 10 and 12 mg/kg/day, respectively (approximately 1.2 and 0.7 times, respectively, the maximum recommended human dose [MRHD] of 80 mg on a mg/m^2 basis), produced no evidence of carcinogenicity.

Teratogenicity
Reproduction studies have been performed with fluoxetine in rats and rabbits at doses 9 and 11 times the maximum daily human dose (80 mg) respectively and have revealed no evidence of harm to the fetus.

Effect on Fertility
Two fertility studies conducted in rats at doses of up to 7.5 and 12.5 mg/kg/day (approximately 0.9 and 1.5 times the maximum recommended human dose on a mg/m^2 basis), indicated that fluoxetine had no adverse effects on fertility.

Use in Pregnancy
No adequate and well-controlled studies have been performed in pregnant women; therefore fluoxetine should not be used during pregnancy unless clearly needed.

Use in Labor and Delivery
The effect of fluoxetine on labor and delivery in humans is unknown. However, because fluoxetine crosses the placenta and because of the possibility that fluoxetine may have adverse effects on the newborn, fluoxetine should be used during labor and delivery only if the potential benefits to the mother justifies the potential risk to the fetus.

Use in Lactation
Because fluoxetine is excreted in human milk, breastfeeding is not recommended.

Use in Pediatrics
Safety and efficacy for use of fluoxetine in children have not been established.

Use in the Elderly
Fluoxetine has not been evaluated extensively in patients over the age of 60. Clinical data are currently insufficient to exclude the possibility of age-related differences during long-term fluoxetine therapy, particularly in elderly patients with systemic disease or those who are receiving other drugs concomitantly.

Use in Patients with Impaired Hepatic Function
Hepatic function impairment can delay the elimination of fluoxetine. Fluoxetine should therefore be used with caution in patients with liver disease. A lower or less frequent dose should be used.

Use in Patients with Impaired Renal Function
Studies in depressed patients on dialysis did not reveal excessive accumulation of fluoxetine or norfluoxetine in plasma. Use of a lower or less frequent dose for renally impaired patients is not routinely necessary.

Adverse Reactions
Commonly Observed
Nervous system complaints (including anxiety, nervousness, and insomnia); drowsiness and fatigue or asthenia; tremor, sweating; gastrointestinal complaints including anorexia, nausea, and diarrhea; dizziness or lightheadedness.
In controlled clinical trials for OCD using fixed doses of 20, 40, or 60 mg daily, adverse events observed at an incidence of at least 5% for fluoxetine and for which the incidence was approximately twice or more the incidence among placebo-treated patients included : somnolence, anxiety, tremor, nausea, dyspepsia, gastrointestinal disorder, vasodilatation, dry mouth, sweating, rash, abnormal vision, yawn, decreased libido and abnormal ejaculation.

Incidence Above or Equal to 1%
Body as a Whole
Asthenia, infection (viral or bacterial), pain, (limb, chest), back pain, fever, chills, malaise, allergic reaction, accidental injury.

Gastrointestinal
Nausea, diarrhea/loose stools, mouth dryness, anorexia, dyspepsia, constipation, abdominal pain, vomiting, taste change, flatulence, increased appetite, GI disorder, melena.

Cardiovascular
Hot flushes, palpitation, vasodilatation, hypertension, chest pain.

Respiratory
Flu-like syndrome, upper respiratory infection, pharyngitis, headache (sinus), dyspnea, bronchitis, rhinitis, sinusitis, cough, nasal congestion, yawn.

Central Nervous System
Headache, drowsiness, tremor, dizziness, fatigue, sleep disorder, sedation, decreased libido, lightheadedness, decreased concentration, abnormal dreams, agitation, myoclonus/twitching, hypertonia, CNS stimulation, confusion, fatigue/malaise, sensation disturbances amnesia, emotional lability, abnormal thinking, sleep disorder, depersonalization. Anxiety, nervousness, and insomnia were reported by 10% to 15% of patients treated with fluoxetine. These symptoms led to drug discontinuation in 5% of patients treated with fluoxetine.

Musculoskeletal
Pain (joint), pain (muscle), myalgia, myasthenia, myopathy, arthralgia.

Dermatological
Excessive sweating, rash, pruritus, acne.

Urogenital
Painful menstruation, sexual dysfunction/impotence, frequent micturition, urinary tract infection.

Special Senses
Vision disturbances/blurred vision, tinnitus, taste perversion, amblyopia.

Miscellaneous
Altered appetite and weight (weight loss or weight gain), lymphadenopathy. Significant weight loss, especially in underweight depressed patients, may be an undesirable result of treatment with fluoxetine. Approximately 9% of patients experienced anorexia. A weight loss of greater than 5% of body weight occurred in 13% of patients treated with fluoxetine compared to 4% of placebo and 3% of patients treated with tricyclics. However, only rarely have patients discontinued treatment with fluoxetine because of weight loss.

Incidence Up to 1%
Body as a Whole
Chills and fever, cyst, facial edema, hangover effect, jaw pain, malaise, neck pain, neck rigidity, pelvic pain, cyst, intentional overdose, suicidal attempt.

Gastrointestinal
Aphthous stomatitis, dysphagia, eructation, esophagitis, gastritis, gingivitis, glossitis, abnormal liver function tests, gum hemorrhage, melena, stomatitis, thirst.

Cardiovascular
Congestive heart failure, angina pectoris, arrhythmia, hemorrhage, hypotension, migraine, postural hypotension, syncope, tachycardia.

Respiratory
Asthma, epistaxis, hiccups, atelectasis, decreased cough, emphysema, hypoventilation, hyperventilation, penumothorax, stridor, pneumonia.

Musculoskeletal
Arthritis, bone pain, bursitis, tenosynovitis, twitching.

Central Nervous System
Abnormal gait, acute brain syndrome, akathisia, amnesia, apathy, ataxia, buccoglossal syndrome, CNS stimulation, neurosis, personality disorder, apathy, ataxia, depersonalization, emotional lability, convulsions, seizures, delusions, euphoria, hallucinations, hostility, hyperkinesia, hypoesthesia, incoordination, increased libido, manic reaction, neuralgia, migraine, neuropathy, paranoid reaction, psychosis, vertigo.

Dermatological
Acne, alopecia, contact dermatitis, dry skin, herpes simplex, maculopapular rash, skin discoloration, skin ulcer, urticaria.

Urogenital
Nocturia, polyuria, abnormal ejaculation, anorgasmia, amenorrhea, breast pain, cystitis, dysuria, fibrocystic breast, leukorrhea, leukorrhea, menopause, menorrhagia, ovarian disorder, urinary incontinence, urinary retention, urinary urgency, impaired urination, vaginitis.

Special Senses
Amblyopia, conjunctivitis, ear pain, eye pain, mydriasis, photophobia, tinnitus.

Activation of Mania/Hypomania
These have occurred in approximately 1% of fluoxetine-treated patients. Activation of mania/hypomania has also been reported in a small proportion of patients with Major Affective Disorder treated with other antidepressants.

Miscellaneous
Anemia, generalized edema, hypoglycemia, hypothyroidism, lymphadenopathy, ecchymosis, hypochromic anemia, lymphedema, thrombocytopenia, peripheral edema, weight gain.

Rarely Reported (less than 0.1%)
Body as a Whole
Enlarged abdomen, abdominal syndrome acute, cellulitis, hydrocephalus, hypothermia, LE syndrome, moniliasis, serum sickness, intentional injury, neuroleptic malignant syndrome, photosensitivity reaction.

Gastrointestinal
Bloody diarrhea, cholecystitis, cholelithiasis, colitis, duodenal ulcer, enteritis, fecal incontinence, hematemesis, biliary pain, esophageal ulcer, GI hemorrhage, hemorrhage of colon, intestinal obstruction, pancreatitis, peptic ulcer, rectal hemorrhage, hyperchlorhydria, increased salivation, mouth ulceration, salivary gland enlargement, stomach ulcer, tongue discoloration, tongue edema.

Cardiovascular
First degree AV block, bradycardia, atrial fibrillation, cerebral embolism, cerebrovascular accident, extrasystoles, heart arrest, heart block, pallor peripheral vascular disorder, phlebitis, shock, thrombosis, vasospasm, ventricular extrasystoles, ventricular fibrillation, bradycardia, bundle branch block, cerebral ischemia, myocardial infarct, thrombophlebitis, vascular headache, ventricular arrhythmia.

Respiratory
Apnea, hemoptysis, hypoxia, larynx edema, lung edema, lung fibrosis/ alveolitis, pleural effusion.

Musculoskeletal
Bone necrosis, chondrodystrophy, muscle hemorrhage, myositis, osteoporosis, pathological fracture, rheumatoid arthritis, osteomyelitis, arthrosis.

Central Nervous System
Abnormal EEG, delusions, foot drop, hyperesthesia, neuritis, antisocial reaction, chronic brain syndrome, circumoral paresthesia, CNS depression, coma, dysarthria, dystonia, extrapyramidal syndrome, hypertonia, hysteria, myoclonus, nystagumus, paralysis, decreased reflexes, increased reflexes, stupor, torticollis, tardive dyskinesia.

Dermatological
Eczema, erythema multiforme, fungal dermatitis, herpes zoster, hirsutism, psoriasis, furunculosis, petechial rash, purpuric rash, pustular rash, seborrhea, skin hypertrophy, subcutaneous nodule, vesiculobullous rash.

Urogenital
Abortion, albuminuria, breast enlargement, dyspareunia, epididymitis, female lactation, hematuria, hypomenorrhea, kidney calculus, metorrhagia, orchitis, polyuria, pyelonephritis, pyuria, salpingitis, urethral pain, urethritis, urinary tract disorder, urolithiasis, uterine hemorrhage, uterine spasm, glycosuira, kidney pain, oliguria, priapism, uterine fibroids enlarged, vaginal/uterine hemorrhage.

Special Senses
Blepharitis, cataract, corneal lesion, deafness, diplopia, eye hemorrhage, glaucoma, iritis, ptosis, exophthalmos, hyperacusis, parosmia, dry eyes, scleritis, visual field defect, strabismus, taste loss.

Miscellaneous
Increased bleeding time, blood dyscrasia, dehydration, goiter, gout, hypercholesterolemia, hyperglycemia, hyperlipemia, hyperthyroidism, hypoglycemic reaction, hypokalemia, hyperkalemia, hyponatremia, hepatitis, liver fatty deposits, hepatomegaly, jaundice, liver tenderness, iron deficiency anemia, leukopenia, lymphocytosis, petechia, purpura, alcohol intolerance, increased sedimentation rate, thrombocytopenia, diabetic acidosis, diabetes mellitus. The following effects were reported in controlled clinical trials with an incidence similar or lesser than placebo:
Viral infection, allergy, influenza, gastroenteritis, palpitations, upper respiratory tract infection, nasal congestion, sinusitis, cough, pain in back, joints and muscles, sensation disturbance.

Precautions
Seizures
Fluoxetine, like other common antidepressants, should be introduced with care in patients with a history of seizures. The incidence of seizures (0.2%) reported with fluoxetine appears to be similar to that associated with these drugs.

Anxiety and Insomnia
In clinical trials for depression, patients reported anxiety, nervousness, or insomnia. In trials for obsessive-compulsive disorder, insomnia and anxiety were also reported.

Altered Appetite and Weight
Significant weight loss, especially in underweight depressed patients, may be an undesirable result of treatment with fluoxetine. In clinical trials for obsessive-compulsive disorder, anorexia was reported.

Activation of Mania/Hypomania
Mania/hypomania were reported in clinical trials for depression, as well as for obsessive- compulsive disorder.

Suicide
The possibility of a suicide attempt is inherent in depression and may persist until significant remission occurs. Close supervision of high-risk patients should accompany initial drug therapy. Prescriptions for fluoxetine should be written for the smallest quantity of capsules consistent with good patient management, in order to reduce the risk of deliberate overdose.

Use in Patients With Concomitant Illness
Clinical experience with fluoxetine in patients with concomitant systemic illness is limited. Caution is advisable in using fluoxetine in patients with diseases or conditions that could affect metabolism or hemodynamic responses.
For use in patients with impaired hepatic function and in patients with impaired renal function, see "Warnings".
In patients with diabetes, fluoxetine may alter glycemic control. Hypoglycemia has occurred during therapy with fluoxetine, and hyperglycemia has developed following discontinuation of the drug. As is true with many other types of medication when taken concurrently by patients with diabetes, insulin and/or oral hypoglycemic dosage may need to be adjusted when therapy with fluoxetine is instituted or discontinued.
Fluoxetine has not been evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or unstable heart disease. However, from the electrocardiograms of some patients who participated in clinical trials, no conduction abnormalities that resulted in heart block were observed. The mean heart rate was reduced by approximately 3 beats/min.

Interference With Cognitive and Motor Performance
Any psychoactive drug may impair judgment, thinking, or motor skills, and patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that the drug treatment does not affect them adversely.

The Long Elimination Half- lives of Fluoxetine and its Metabolites
Because of the long elimination half-lives of the parent drug and 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.

Hyponatremia
Several cases of hyponatremia (some with serum sodium lower than 110 mmol/L) have been reported. The hyponatremia appeared to be reversible when fluoxetine was discontinued. Although these cases were complex with varying possible etiologies, some were possibly due to the syndrome of inappropriate antidiuretic hormone secretion (SIADH). The majority of these occurrences have been in older patients and in patients taking diuretics or who were otherwise volume-depleted.

Platelet Function
There have been rare reports of altered platelet function and/or abnormal results from laboratory studies in patients taking fluoxetine. While there have been reports of abnormal bleeding in several patients taking fluoxetine, it is unclear whether fluoxetine had a causative role.

Drug Interactions
Note
Drugs Metabolized by P450IID6
Approximately 3% to 10% of the normal population has a genetic defect that leads to reduced levels of activity of the cytochrome P450 isoenzyme P450IID6. Such individuals have been referred to as "poor metabolizers" of drugs such as dextromethorphan, and tricyclic anti- depressants. Many drugs, such as most antidepressants including fluoxetine and other selective uptake inhibitors of serotonin, are metabolized by this isoenzyme; thus, both the pharmacokinetic properties and relative proportion of metabolites are altered in poor metabolizers.
Fluoxetine, like other agents including most antidepressants, inhibits the activity of the isoenzyme P450IID6. Thus, fluoxetine reduces the elimination of medications which are predominantly metabolized by the P450IID6 system. Dose adjustments for such medications are required when taken concurrently with fluoxetine or within 5 weeks after discontinuation of its use.

Drugs with a narrow therapeutic index represent the greatest concern (e.g., flecainide, encainide, vinblastine, carbamazepine, and tricyclic antidepressants).

Drugs Metabolized by P450IIIA4
In an in vivo interaction study involving coadministration of fluoxetine with single doses of terfenadine (a cytochrome P450IIIA4 substrate), no increase in plasma terfenadine concentrations occurred with concomitant fluoxetine. In addition, in vitro studies have shown ketoconazole, a potent inhibitor of P450IIIA4 activity, to be at least 100 times more potent than fluoxetine or norfluoxetine as an inhibitor of the metabolism of several substrates for this enzyme, including astemizole, cisapride, and midazolam. These data indicate that fluoxetine's extent of inhibition of cytochrome P450IIIA4 is not likely to be of clinical significance.

Fluoxetine/Tryptophan: Patients receiving fluoxetine in combination with tryptophan experienced adverse reactions, including agitation, restlessness, and gastrointestinal distress.

Fluoxetine/Monoamine Oxidase Inhibitors: See Contraindications.

Fluoxetine/Other Antidepressants: There have been greater than 2-fold increases of previously stable plasma levels of other antidepressants when fluoxetine has been administered in combination with these agents.

Fluoxetine/Antipsychotics (e.g., Haloperidol, Pimozide, Clozapine): Some clinical data suggests a possible pharmacodynamic and/or pharmacokinetic interaction between serotonin specific reuptake inhibitors (SSRIs) and antipsychotics. Elevation of blood levels of haloperidol and clozapine has been observed in patients receiving concomitant fluoxetine. A single case report has suggested possible additive effects of pimozide and fluoxetine leading to bradycardia.

Fluoxetine/Lithium: There have been reports of both increased and decreased lithium levels when lithium was used concomitantly with fluoxetine. Cases of lithium toxicity have been reported. Lithium levels should be monitored when these drugs are administered concomitantly.

Fluoxetine/Benzodiazepines (Including Diazepam, Alprazolam): The half-life of concurrently administered diazepam may be prolonged in some patients. Coadministration of alprazolam and fluoxetine has resulted in increased alprazolam plasma concentrations and in further psychomotor performance decrement due to increased plasma alprazolam levels.

Fluoxetine/Phenytoin/Carbamazepine: Patients on stable doses of phenytoin and carbamazepine have developed elevated plasma anticonvulsant concentrations and clinical anticonvulsant toxicity following initiation of concomitant fluoxetine treatment.

Fluoxetine/Highly Protein-Bound Drugs: 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. Conversely, adverse effects may result from displacement of protein bound fluoxetine by other tightly bound drugs.

Fluoxetine/Warfarin: Altered anticoagulant effects, including increased bleeding, have been reported when fluoxetine is coadministered with warfarin. Patients receiving warfarin therapy should receive careful coagulation monitoring when fluoxetine is initiated or stopped.

Fluoxetine/CNS Active Drugs: The risk of using fluoxetine in combination with other CNS active drugs has not been systematically evaluated. Consequently, caution is advised if the concomitant administration of fluoxetine and such drugs is required.

Therapeutic Interaction
Fluoxetine/Electroconvulsive Therapy (ECT): There are no clinical studies establishing the benefit of the combined use of fluoxetine and ECT. There have been rare reports of prolonged seizures in patients on fluoxetine receiving ECT treatment.

Laboratory Test Abnormalities (Incidence less than 0.1%)
Increased alkaline phosphatase, increased BUN, increased creatine phosphokinase, hyperuricemia, hypocalcemia, increased alanine aminotransferase (ALT).

Information for Patients
Fluoxetine may impair judgment, thinking, or motor skills; therefore 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 drugs, or alcohol.
Patients should be advised to notify their physician if they become pregnant, intend to become pregnant during therapy, or if they are breastfeeding.
Patients should be advised to notify their physician if they develop a rash or hives.

Dosage and Administration
Because of the long elimination half-lives of the parent drug and its major active metabolite, changes in dose will not be fully reflected in plasma levels for several weeks. Therefore, monitoring of plasma levels may not be a good indicator for dose adjustments of fluoxetine.

Treatment of Depression
Initial Therapy
The recommended dose is 20 mg/day administered in the morning.
A dose increase may be considered after several weeks if no clinical improvement is observed. Doses above 20 mg/day should be administered on a b.i.d. schedule (i.e., morning and noon) and should not exceed a maximum dose of 80 mg/day.
The full antidepressant effect may be delayed until 4 weeks of treatment or longer.
As with many other medications, a lower or less frequent dosage should be used in patients with hepatic impairment. A lower or less frequent dosage should also be considered for the elderly and for patients with concurrent disease or on multiple medications. Dosage adjustments for renal impairment are not routinely necessary.

Maintenance/Long-Term Treatment
Optimal duration of fluoxetine therapy remains speculative. Acute episodes of depression generally require several months or longer of sustained pharmacologic therapy; whether the dose of antidepressant needed to induce remission is identical to the dose needed to maintain or sustain mental tranquillity is unknown.

Treatment of Obsessive -Compulsive Disorder (OCD)
Initial Therapy
The initial recommended dose is 20 mg once daily administered in the morning.
The dose may be then gradually increased up to 60 mg daily after several weeks of non- satisfactory response to the initial dose. The maximum daily dosage should not exceed 80 mg. As with the use of Fluoxetine in depression, a lower or less frequent dosage should be used in patients with renal hepatic impairment. A lower or less frequent dosage should also be considered for the elderly (see Use in the Elderly under Warnings,), and for patients with concurrent disease or on multiple medications. Dosage adjustments for renal impairment are not routinely necessary.

Maintenance/Continuation Therapy
While there are no systematic studies that answer the question for how long to continue fluoxetine, OCD is a chronic condition and it is reasonable to consider continuation for a responding patient. Although the efficacy of fluoxetine after 13 weeks has not been documented in controlled trials, patients have been continued in therapy under double-blind conditions for up to an additional 6 months without loss of benefit. However, 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.

Treatment of Binge-Eating and Vomiting Behaviors in Bulimia Nervosa. (Reduction of Binge-Eating and Purging Activity)
Initial Therapy
A dose of 60 mg/day is recommended, administered in the morning. For some patients it may be advisable to titrate up to this target dose over several days. Fluoxetine doses above 60 mg/day have not been systematically studied in patients with bulimia.
As with the use of fluoxetine in depression and OCD, a lower or less frequent dosage should be used in patients with hepatic impairment. A lower or less frequent dosage should also be considered for the elderly, and for patients with concurrent disease or on multiple concomitant medications. Dosage adjustments for renal impairment are not routinely necessary.

Maintenance/Continuation Therapy
While there are no systematic studies that answer the question of how long to continue fluoxetine, bulimia is a chronic condition and it is reasonable to consider continuation for a responding patient. Although the efficacy of fluoxetine after 16 weeks has not been documented in controlled trials, some patients have been continued in therapy under double-blind conditions for up to an additional 6 months without loss of benefit. However, patients should be periodically reassessed to determine the need for continued treatment.

Overdosage
There have been 2 deaths among approximately 38 reports of acute overdose with fluoxetine, either alone or in combination with other drugs or alcohol. One death involved a combined overdose with approximately 1.8 g fluoxetine and an undetermined amount of maprotiline. A second death involved 3 drugs. One patient who took 3 g fluoxetine experienced 2 grand mal seizures that remitted spontaneously without specific anticonvulsant treatment. The actual amount of drug absorbed may have been less due to vomiting.

Manifestations
Nausea and vomiting were prominent in overdosages involving higher fluoxetine doses. Other prominent symptoms of overdosage included agitation, restlessness, hypomania, and other signs of CNS excitation.

Treatment
There are no specific antidotes. Establish and maintain an airway; ensure adequate oxygenation and ventilation. Activated charcoal, which may be used with sorbitol, may be as more effective than emesis or lavage, and should be considered in treating overdosage. Cardiac and vital signs monitoring is recommended, along with general symptomatic and supportive measures. Based on experience in animals, which may not be relevant to humans, SSRI-induced seizures that fail to remit spontaneously may respond to diazepam. Due to the large volume of distribution of fluoxetine, forced diuresis, dialysis, hemoperfusion, and exchange transfusion are unlikely to be of benefit.
In managing overdosage, consider the possibility of multiple drug involvement. A specific caution involves patients taking or recently having taken fluoxetine who might ingest by accident or intent, excessive quantities of a tricyclic antidepressant. In such a case, accumulation of the parent tricyclic and an active metabolite may increase the possibility of clinically significant sequelae and extend the time needed for close medical observation.

Presentation
Fluoxetine 20 Packs of 30 capsules.

Manufacturer: Teva Pharmaceutical Industries Ltd, Israel

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