PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

[Pr]Teva-Fluoxetine

Fluoxetine Capsules

capsules, 10 mg and 20 mg fluoxetine (as fluoxetine hydrochloride), oral

USP

Antidepressant / Antiobsessional / Antibulimic

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RECENT MAJOR LABEL CHANGES

7 Warnings and Precautions	04/2022
7 Warnings and Precautions, 7.1.1 Pregnant Women	04/2022

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Sections or subsections that are not applicable at the time of authorization are not listed.

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

Teva-Fluoxetine (fluoxetine) is indicated in adults for:

- Depression*:*
  Teva-Fluoxetine is indicated for the symptomatic relief of Major Depressive Disorder (MDD).

- Bulimia Nervosa**:**
  Fluoxetine has been shown to significantly decrease binge-eating and purging activity when compared with placebo treatment.

- Obsessive-Compulsive Disorder (OCD):
  Teva-Fluoxetine is indicated for the symptomatic treatment of obsessive-compulsive disorder (OCD).
  The obsessions or compulsions must be experienced as intrusive, markedly distressing, time consuming, or interfering significantly with the person's social or occupational functioning.

The efficacy of fluoxetine in hospitalized patients has not been adequately studied.

Long-term use of Teva-Fluoxetine: The effectiveness of fluoxetine in long-term use in bulimia nervosa (i.e. for more than 16 weeks) and in obsessive-compulsive disorder (i.e. for more than 13 weeks) has not been systematically evaluated in controlled trials. Therefore, the health professional who elects to use Teva-Fluoxetine in these indications for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient.

1.1 Pediatrics

Pediatrics (<18 years of age)**:** No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use. See 7 WARNINGS AND PRECAUTIONS, General, Potential Association with Behavioural and Emotional Changes, including Self-Harm; see also 8.2.1. Clinical Trial Adverse Reactions – Pediatrics.

1.2 Geriatrics

Geriatrics (≥ 60 years of age): Evidence from clinical studies and experience suggests that use in the geriatric population may be associated with differences in safety or effectiveness, and a brief discussion can be found in the appropriate sections (4.2. Recommended Dose & Dosage Adjustment, Special Patient Populations; 7.1.4 Geriatrics).

2 CONTRAINDICATIONS

- *Hypersensitivity* -Teva-Fluoxetine (fluoxetine) is contraindicated in patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING section.

- Monoamine Oxidase Inhibitors - In patients receiving serotonin reuptake inhibitors (SSRIs) in combination with a monoamine oxidase inhibitor (MAOI), there have been reports of serious, sometimes fatal, reactions (including hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, and mental status changes that include extreme agitation progressing to delirium and coma). These reactions have also been reported in patients who have recently discontinued SSRI treatment and then started treatment on an MAOI. Some cases presented with features resembling neuroleptic malignant syndrome (e.g., serotonin syndrome). Teva-Fluoxetine should not be used in combination with an MAOI (including the antibiotic linezolid and the thiazine dye methylthioninium chloride (methylene blue) which are less well-known examples of MAOIs) or within 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 elapse after discontinuing treatment with Teva-Fluoxetine before starting an MAOI. Limited reports suggest that intravenously administered dantrolene or orally administered cyproheptadine may benefit patients experiencing such reactions. See 9.4 Drug-Drug Interactions, Monoamine-Oxidase Inhibitors section.

- *Thioridazine* - Thioridazine should not be administered concomitantly with Teva-Fluoxetine or within a minimum of 5 weeks after Teva-Fluoxetine has been discontinued, nor should Teva-Fluoxetine be administered within 2 weeks after thioridazine has been discontinued.

  Thioridazine administration alone produces prolongation of the QTc interval, which is associated with serious ventricular arrhythmias, such as torsades de pointes-type arrhythmias, and sudden death. This effect appears to be dose-related.

  An *in vivo* study suggests that drugs which inhibit P4502D6, including certain SSRI's such as paroxetine, fluoxetine and fluvoxamine, will elevate plasma levels of thioridazine. Therefore, fluoxetine should not be used in combination with thioridazine. See 9.4 Drug-Drug Interactions, Thioridazine section.

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

General:
During maintenance therapy, the dosage should be kept at the lowest effective level.

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 Teva-Fluoxetine is coadministered or has been recently discontinued (see 9.4 Drug-Drug Interactions, Tricyclic Antidepressants section).

Switching Patients to or from a Monoamine Oxidase Inhibitor (MAOI):
At least 14 days should elapse between discontinuation of an MAOI and initiation of therapy with Teva-Fluoxetine. In addition, at least 5 weeks, perhaps longer, should be allowed after stopping Teva-Fluoxetine before starting MAOI (see 2 CONTRAINDICATIONS section).

Discontinuation of Treatment:
When dosing is stopped, active drug substances will persist in the body for weeks. This should be borne in mind when starting or stopping treatment. Dosage tapering is unnecessary in most patients.

Despite its long-half life, symptoms associated with the discontinuation of fluoxetine have been reported in clinical trials and post-marketing. Patients should be monitored for these and other symptoms when discontinuing treatment, regardless of the indication for which Teva-Fluoxetine is being prescribed. fluoxetine has been only rarely associated with such symptoms. Plasma fluoxetine and norfluoxetine concentrations decrease gradually at the conclusion of therapy, which makes dose tapering unnecessary in most patients (See 7 WARNINGS AND PRECAUTIONS and 8.1 Adverse Reaction Overview).

4.2 Recommended Dose and Dosage Adjustment

Depression:
Initial Adult Dosage: The usual initial dosage is 20 mg administered once daily in the morning. A gradual dose increase should be considered only after a trial period of several weeks if the expected clinical improvement does not occur. Dosage should not exceed a maximum of 60 mg per day.

Long Term: The efficacy of fluoxetine in maintaining an antidepressant response for up to 38 weeks following 12 weeks of open-label acute treatment (50 weeks total) was demonstrated in a placebo-controlled trial. The usefulness of the drug in patients receiving fluoxetine for extended periods should be reevaluated periodically (see 14.1 Trial Design and Study Demographics section).

Bulimia Nervosa:
Adult Dosage: The recommended dosage is 60 mg per day, although studies show that lower doses may also be efficacious. Electrolyte levels should be assessed prior to initiation of treatment.

Obsessive-Compulsive Disorder:
A dose range of 20 mg/day to 60 mg/day is recommended for the treatment of obsessive-compulsive disorder.

Dose Adjustment:
Since it may take up to four or five weeks to reach steady-state plasma levels of fluoxetine, sufficient time should be allowed to elapse before dosage is gradually increased. Higher dosages are usually associated with an increased incidence of adverse reactions.

Special Patient Populations:
For any indication:

- Use in Pregnant Women:
  Results of a number of epidemiological studies of pregnancy outcomes following early maternal exposure to antidepressants have been inconsistent, but there is some evidence of a possible small increase in the risk of cardiac malformations (e.g., ventricular and septal defects) associated with use of fluoxetine. The mechanism is unknown. The use of Teva-Fluoxetine during pregnancy should be considered only if the potential benefit justifies the potential risk to the fetus taking into account the risks associated with untreated depression.
  Post-marketing reports indicate that some neonates exposed to fluoxetine, SSRIs or other newer anti-depressants, late in the third trimester have developed complications requiring prolonged hospitalization, respiratory support, and tube feeding (see 7.1 Special Populations, 7.1.1 Pregnant Women, Complications following late third trimester exposure to SSRIs). When treating pregnant women with Teva-Fluoxetine during the third trimester, the health professional should carefully consider the potential risks and benefits of treatment. The health professional may consider tapering Teva-Fluoxetine in the third trimester.

- **Geriatrics (≥ 60 years of age)**: Fluoxetine was evaluated in depressed elderly patients only at a dosage of 20 mg/day. A lower or less frequent dosage may be effective and should be considered in elderly patients with concurrent disease or on multiple medications.

- **Pediatrics (<18 years of age):** Health Canada has not authorized an indication for pediatric use (see 7 WARNINGS AND PRECAUTIONS, General, Potential Association with Behavioural and Emotional Changes, including Self-Harm).

- **Renal/Hepatic Impairment or Otherwise Debilitated Patients:** A lower or less frequent dosage should be used in patients with renal and/or hepatic impairment and in those on multiple medications.

4.4 Administration

Teva-Fluoxetine may be taken with or without food. The capsules should not be opened or chewed, and they must be swallowed whole.

4.5 Missed Dose

In the event that a patient misses a dose, they should be instructed to take their dose as soon as they can. The next dose should be taken at the next scheduled time.

5 OVERDOSAGE

Signs and Symptoms:
Cases of overdose of fluoxetine alone usually have a mild course. Symptoms of overdose included nausea, vomiting, seizures, cardiovascular dysfunction ranging from asymptomatic arrhythmias (including nodal rhythm and ventricular arrhythmias) or ECG changes indicative of QTc prolongation to cardiac arrest (including very rare cases of Torsade de Pointes), pulmonary dysfunction, and signs of altered CNS status ranging from excitation to coma. Fatalities attributed to overdose of fluoxetine alone have been reported. (Please refer to Human Experience and Animal Experience sections below).

Management of Overdosage:
There are no specific antidotes for fluoxetine.

Treatment should consist of those general measures employed in the management of overdosage with any antidepressant.

Establish and maintain an airway; ensure adequate oxygenation and ventilation.

Cardiac, electrocardiogram, and vital signs monitoring is recommended, along with general symptomatic and supportive measures.

Induction of emesis is not recommended.

Gastric lavage with a large-bore orogastric tube with appropriate airway protection, if needed, may be indicated if performed soon after ingestion, or in symptomatic patients.

Activated charcoal should be considered in treating overdose.

Due to the large volume of distribution of fluoxetine, forced diuresis, dialysis, hemoperfusion, and exchange transfusion are unlikely to be of benefit.

A specific caution involves patients who are taking or have recently taken fluoxetine and might ingest excessive quantities of a TCA. In such a case, accumulation of the parent tricyclic and/or an active metabolite may increase the possibility of clinically significant sequelae and extend the time needed for close medical observation.

Fluoxetine-induced seizures which fail to remit spontaneously may respond to diazepam. (see Product Monograph for diazepam).

In managing overdosage, consider the possibility of multiple drug involvement. The health professional should consider contacting a poison control centre on the treatment of any overdosage.

Human Experience:
Worldwide exposure to fluoxetine hydrochloride is estimated to be over 38 million patients (circa 1999). Of the 1578 cases of overdose involving fluoxetine hydrochloride, alone or with other drugs, reported from this population, there were 195 deaths.

Among 633 adult patients who overdosed on fluoxetine hydrochloride alone, 34 resulted in a fatal outcome, 378 completely recovered, and 15 patients experienced sequelae after overdosage, including abnormal accommodation, abnormal gait, confusion, unresponsiveness, nervousness, pulmonary dysfunction, vertigo, tremor, elevated blood pressure, impotence, movement disorder, and hypomania. The remaining 206 patients had an unknown outcome. The most common signs and symptoms associated with non-fatal overdosage were seizures, somnolence, nausea, tachycardia, and vomiting. The largest known ingestion of fluoxetine hydrochloride in adult patients was 8 grams in a patient who took fluoxetine alone and who subsequently recovered.
However, in an adult patient who took fluoxetine alone, an ingestion as low as 520 mg has been associated with lethal outcome, but causality has not been established.

Among pediatric patients (ages 3 months to 17 years), there were 156 cases of overdose involving fluoxetine alone or in combination with other drugs. Six patients died, 127 patients completely recovered, 1 patient experienced renal failure, and 22 patients had an unknown outcome. One of the six fatalities was a 9-year-old boy who had a history of OCD, Tourette's syndrome with tics, attention deficit disorder, and fetal alcohol syndrome. He had been receiving 100 mg of fluoxetine daily for 6 months in addition to clonidine, methylphenidate, and promethazine. Mixed-drug ingestion or other methods of suicide complicated all six overdoses in children that resulted in fatalities. The largest ingestion in pediatric patients was 3 grams which was non-lethal.

Other important adverse events reported with fluoxetine overdose (single and multiple drugs) include coma, delirium, ECG abnormalities (such as QT interval prolongation and ventricular

tachycardia, including torsades de pointes-type arrhythmias), hypotension, mania, neuroleptic malignant syndrome-like events, pyrexia stupor, and syncope.

Animal Experience:
Studies in animals do not provide precise or necessarily valid information about the treatment of human overdose.

However, animal experiments can provide useful insights into possible treatment strategies.

The oral median lethal dose in rats and mice was found to be 452 and 248 mg/kg, respectively. Acute high oral doses produced hyper-irritability and convulsions in several animal species.

Among six dogs purposely overdosed with oral fluoxetine, five experienced grand mal seizures. Seizures stopped immediately upon the bolus intravenous administration of a standard veterinary dose of diazepam. In this short-term study, the lowest plasma concentration at which a seizure occurred was only twice the maximum plasma concentration seen in humans taking 80 mg/day, chronically.

In a separate single-dose study, the ECG of dogs given high doses did not reveal prolongation of the PR, QRS, or QT intervals. Tachycardia and an increase in blood pressure were observed. Consequently, the value of the ECG in predicting cardiac toxicity is unknown. Nonetheless, the ECG should ordinarily be monitored in cases of human overdose.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 1 – Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Oral	Capsules / 10 mg and 20 mg	Teva-Fluoxetine 10mg capsules contain: colloidal silicon dioxide, magnesium stearate, pregelatinized starch and sodium starch glycolate. The capsule shell contains: D & C yellow # 10, FD& C blue #1, FD & C yellow #6, gelatin, iron oxide black and titanium dioxide. Teva-Fluoxetine 20mg capsules contain: colloidal silicon dioxide, magnesium stearate, pregelatinized starch and

		sodium starch glycolate. The capsule shell contains: D & C yellow # 10, FD& C blue #1, FD & C yellow #6, gelatin and titanium dioxide.

Availability of Dosage Forms:

10mg: hard gelatin capsules with opaque green cap and opaque grey body, imprinted with black ink **novo** on cap and **10** on body containing fluoxetine hydrochloride equivalent to 10 mg of fluoxetine.
Bottles of 100.

20mg: hard gelatin capsules with opaque light green cap and opaque ivory body, imprinted with black ink **novo** on cap, **20** on body, containing fluoxetine hydrochloride equivalent to 20 mg of fluoxetine. Bottles of 100 and 500.

7 WARNINGS AND PRECAUTIONS

General

POTENTIAL ASSOCIATION WITH BEHAVIOURAL AND EMOTIONAL CHANGES, INCLUDING SELF-HARM

Pediatrics - Placebo-Controlled Clinical Trial Data

Recent analyses of placebo-controlled clinical trial safety databases from selective serotonin reuptake inhibitors (SSRIs) and other newer anti-depressants suggests that use of these drugs in patients under the age of 18 may be associated with behavioural and emotional changes, including an increased risk of suicidal ideation and behaviour over that of placebo.

The small denominators in the clinical trial database, as well as the variability in placebo rates, preclude reliable conclusions on the relative safety profiles among these drugs.

Adults and Pediatrics - Additional data

There are clinical trial and post-marketing reports with SSRIs and other newer anti-depressants, in both pediatrics and adults, of severe agitation-type adverse events coupled with self-harm or harm to others. The agitation-type events include: akathisia, agitation, disinhibition, emotional lability, hostility, aggression, depersonalization. In some cases, the events occurred within several weeks of starting treatment.

Rigorous clinical monitoring for suicidal ideation or other indicators of potential for suicidal behaviour is advised in patients of all ages. This includes monitoring for agitation-type emotional and behavioural changes. An FDA meta-analysis of placebo-controlled clinical trials of antidepressant drugs in adult patients ages 18 to 24 years with psychiatric disorders showed an increased risk of suicidal behavior with antidepressants compared to placebo.

Families and caregivers of patients being treated with Teva-Fluoxetine should be alerted about the need to monitor patients for the emergence of agitation, anxiety, panic attacks, hostility, irritability, hypomania or mania, unusual changes in behaviour, and other symptoms, as well as the emergence of suicidality particularly within several weeks of starting treatment or changing the dose. Such symptoms should be reported immediately to healthcare providers. Such monitoring should include daily observation by families and caregivers.

Discontinuation Symptoms

Patients currently taking SSRIs or newer anti-depressants should NOT be discontinued abruptly, due to risk of discontinuation symptoms. Fluoxetine has only rarely been associated with such symptoms. At the time that a medical decision is made to discontinue an SSRI or other newer anti-depressant drug, a gradual reduction in the dose rather than an abrupt cessation, except for fluoxetine, is recommended. Plasma fluoxetine and norfluoxetine concentrations decrease gradually at the conclusion of therapy which makes dose tapering unnecessary in most patients taking this drug (see 4.1 Dosing Considerations, Discontinuation of Treatment section; 7 WARNINGS AND PRECAUTIONS, Dependence/Tolerance**;** 8.1 Adverse Reaction Overview, Adverse Events Subsequent to Discontinuation section **).**

Implications of the Long Elimination Half-Life of Fluoxetine

Because of the long elimination half-lives of fluoxetine and its major active metabolite norfluoxetine, 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 (see 4 DOSAGE AND ADMINISTRATION; and 10 CLINICAL PHARMACOLOGY sections). Even when dosing is stopped, active drug substance will persist in the body for weeks due to the long elimination half-lives of fluoxetine and norfluoxetine. This is of potential consequence when drug discontinuation is required or when drugs are prescribed that might interact with fluoxetine and norfluoxetine following discontinuation of Teva-Fluoxetine.

Use of Fluoxetine in Pregnant Women: Effects on Newborns

Results of a number of epidemiological studies of pregnancy outcomes following early maternal exposure to antidepressants have been inconsistent, but there is some evidence of a possible small increase in the risk of cardiac malformations (e.g., ventricular and septal defects) associated with use of fluoxetine. The mechanism is unknown. The use of Teva-Fluoxetine during pregnancy should be considered only if the potential benefit justifies the potential risk to the fetus taking into account the risks associated with untreated depression.

Post-marketing reports indicate that some neonates exposed to fluoxetine, other SSRIs (selective serotonin reuptake inhibitors), or newer anti-depressants late in the third trimester have developed complications requiring prolonged hospitalization, respiratory support, and tube feeding. Such complications can arise immediately upon delivery. When treating a pregnant woman with Teva-Fluoxetine during the third trimester, the physician should carefully consider the potential risks and benefits of treatment. See 4.2 Recommended Dose and Dosage

Adjustment, Special Patient Populations; and 7.1 Special Populations, 7.1.1 Pregnant Women, Complications following late third trimester exposure to SSRIs sections.

Weight Change
Significant weight loss, especially in underweight depressed patients and the elderly, may be an undesirable result of treatment with Teva-Fluoxetine. Teva-Fluoxetine should be given with caution to patients suffering from anorexia nervosa and only if the expected benefits (e.g., co-morbid depression) markedly outweigh the potential weight reducing effect of the drug.

Potential for reduced efficacy of tamoxifen with concomitant SSRI use, including fluoxetine
The antitumor agent tamoxifen is a pro-drug requiring metabolic activation by CYP2D6. Inhibition of CYP2D6 can lead to reduced plasma concentrations of a primary active metabolite (endoxifen). Chronic use of CYP2D6 inhibitors, including certain SSRIs, together with tamoxifen can lead to persistent reduction in levels of endoxifen (see also 9.4 Drug-Drug Interactions). Reduced efficacy of tamoxifen has been reported with concomitant usage of some SSRI antidepressants in some studies. When tamoxifen is used for the treatment of breast cancer, prescribers should consider using an alternative antidepressant with little or no CYP2D6 inhibition.

Carcinogenesis and Mutagenesis:
For animal data, see 16 NON-CLINICAL TOXICOLOGY section.

Cardiovascular
Fluoxetine is associated with a risk of QTc interval prolongation (see 8.4 Abnormal laboratory findings; 9.4 Drug-Drug Interactions, QTc-Prolonging Drugs; 10.2 Pharmacodynamics, Electrocardiography). Rare events of torsade de pointes, ventricular fibrillation, cardiac arrest, and sudden death have been reported with fluoxetine during post-market use (see 8.5 Post-Market Adverse Reactions). If sustained, torsade de pointes can progress to ventricular fibrillation and sudden cardiac death.

Teva-Fluoxetine should be used with caution in patients with conditions such as congenital long QT syndrome and acquired long QT syndrome (e.g., due to concomitant use of a drug that prolongs the QT); a family history of QT prolongation; or other clinical conditions that predispose to arrhythmias (e.g., hypokalemia or hypomagnesemia or hypocalcemia) or increased exposure to fluoxetine (e.g., hepatic impairment). Electrocardiogram monitoring may be warranted in patients who are suspected to be at an increased risk of experiencing torsade de pointes, such as cardiac disease (e.g., ischemic heart disease, congestive heart failure, history of arrhythmias), a family history of QT prolongation, recent myocardial infarction, bradyarrhythmias, patients on concomitant medications that prolong the QTc interval or other clinical conditions that predispose to arrhythmias (e.g., acute neurological events, diabetes mellitus, autonomic neuropathy). Female gender and age 65 years or older are risk factors for torsade de pointes.

When drugs that prolong the QTc interval are prescribed, health professionals should counsel their patients concerning the nature and implications of the ECG changes, underlying diseases and disorders that are considered to represent risk factors, demonstrated and predicted drug-drug interactions, symptoms suggestive of arrhythmia, risk management strategies, and other information relevant to the use of the drug.

Fluoxetine has not been evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or unstable heart disease. Patients with these diagnoses were systematically excluded from premarketing clinical studies. The mean heart rate was reduced by approximately 3 beats/minute.

Hypokalemia
Self-induced vomiting often leads to hypokalemia which may lower seizure threshold and/or may lead to cardiac conduction abnormalities. Electrolyte levels of bulimic patients should be assessed prior to initiation of treatment and at regular intervals thereafter.

Concomitant Illness:
Clinical experience with fluoxetine in patients with concomitant systemic illness is limited and it should be used cautiously in such patients, especially those with diseases or conditions that could affect metabolism or hemodynamic responses.

Dependence/Tolerance:
Discontinuation of Treatment with fluoxetine (Post-Marketing and Clinical Trials)
When discontinuing treatment, patients should be monitored for symptoms which may be associated with discontinuation (e.g., headache, insomnia, paresthesias, nervousness, anxiety, nausea, sweating, numbness, dizziness, jitteriness, asthenia or other symptoms which may be of clinical significance).

Fluoxetine has been only rarely associated with such symptoms. Plasma fluoxetine and norfluoxetine concentrations decrease gradually at the conclusion of therapy, which makes dose tapering unnecessary in most patients (see 4 DOSAGE AND ADMINISTRATION, 7 WARNINGS AND PRECAUTIONS, General; and 8.1 Adverse Reaction Overview).

Dependence Liability
Fluoxetine has not been systematically studied, in animals or humans, for its potential for abuse, tolerance, or physical dependence. Health professionals should carefully evaluate patients for history of drug abuse and follow such patients closely, observing them for signs of misuse or abuse of Teva-Fluoxetine.

Driving and Operating Machinery
Psychomotor Impairment: Patients should be cautioned against driving an automobile or performing hazardous tasks until they are reasonably certain that treatment with Teva-Fluoxetine does not affect them adversely.

Endocrine and Metabolism:

Diabetes

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.

Hematologic

Abnormal Bleeding:

SSRIs and SNRIs, including fluoxetine, may increase the risk of bleeding events by causing abnormal platelet aggregation. Concomitant use of acetylsalicylic acid (ASA), nonsteroidal anti-inflammatory drugs (NSAIDs), warfarin and other anticoagulants may add to the risk. Case reports and epidemiological studies (case-control and cohort design) have demonstrated an association between use of drugs that interfere with serotonin reuptake and the occurrence of gastrointestinal bleeding. Bleeding events related to SSRIs and SNRIs use have ranged from ecchymoses, hematomas, epistaxis, and petechiae to life-threatening hemorrhages.

SSRIs and SNRIs, including fluoxetine, may increase the risk of postpartum hemorrhage (7.1 Special Populations, 7.1.1 Pregnant Women, Complications following late third trimester exposure to SSRIs).

Patients should be cautioned about the risk of bleeding associated with the concomitant use of fluoxetine and NSAIDs, ASA, or other drugs that affect coagulation (see 9.4 Drug-Drug Interactions, Drugs Affecting Platelet Function). Caution is advised in patients with a history of bleeding disorder or predisposing conditions (e.g., thrombocytopenia).

Hepatic/Biliary/Pancreatic

Hepatic Impairment

Since clearances of fluoxetine and norfluoxetine may be decreased in patients with impaired liver function including cirrhosis, a lower or less frequent dose should be used in such patients. See 10.3 Pharmacokinetics, Special Populations and Conditions section.

Immune

Allergic Reactions (Rash and Accompanying Events): During premarketing testing, 7% of 10,782 patients developed various types of rashes 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. Clinical findings reported in association with these allergic reactions include rash, fever, leukocytosis, arthralgias, edema, carpal tunnel syndrome, respiratory distress, lymphadenopathy, proteinuria, and mild transaminase elevation. Most patients improved promptly with discontinuation of fluoxetine and/or adjunctive treatment with antihistamines or steroids, and all patients experiencing these events were reported to recover completely.

In premarketing clinical trials two patients are known to have developed a serious cutaneous systemic illness. In neither patient was there an unequivocal diagnosis, but one was considered to have a leukocytoclastic vasculitis, and the other severe desquamation that was considered variously to be a vasculitis or erythema multiforme. Other patients have had systemic manifestations suggestive of serum sickness.

Since the introduction of fluoxetine, systemic events, possibly related to vasculitis, and including lupus-like syndrome, have developed in patients with rash. Although these events are rare, they may be serious, involving the lung, kidney, or liver. Death has been reported to occur in association with these systemic events.

Anaphylactoid events, including bronchospasm, angioedema, laryngospasm and urticaria alone and in combination, have been reported.

Pulmonary events, including inflammatory processes of varying histopathology and/or fibrosis, have been reported rarely. These events have occurred with dyspnea as the only preceding symptom.

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, Teva-Fluoxetine should be discontinued. Particular caution should be exercised in patients with a history of allergic reactions.

Musculoskeletal

Bone Fracture Risk

An increased risk of bone fractures following exposure to some antidepressants, including SSRIs/SNRIs, was shown by epidemiological studies. The risks appear to be greater at the initial stages of treatment, but significant increased risks were also observed at later stages of treatment. The possibility of fracture should be considered in the care of patients treated with fluoxetine. Elderly patients and patients with important risk factors for bone fractures should be advised of possible adverse events which increase the risk of falls, such as dizziness and orthostatic hypotension, especially at the early stages of treatment but also soon after withdrawal. Preliminary data from observational studies show association of SSRIs/SNRIs and low bone mineral density in older men and women. Until further information becomes available, a possible effect on bone mineral density with long term treatment with SSRIs/SNRIs, including fluoxetine, cannot be excluded, and may be a potential concern for patients with osteoporosis or major risk factors for bone fractures.

Neurologic

Seizures

Teva-Fluoxetine should be used with caution in patients with a history of convulsive disorders. The incidence of seizures associated with fluoxetine during clinical trials did not appear to differ

from that reported with other marketed antidepressants; however, patients with a history of convulsive disorders were excluded from these trials.

Concurrent administration with electroshock therapy should be avoided because of the absence of experience in this area. There have been rare reports of prolonged seizures in patients on fluoxetine receiving ECT treatment.

Serotonin Syndrome /Neuroleptic Malignant Syndrome

On rare occasions serotonin syndrome or neuroleptic malignant syndrome-like events have occurred in association with treatment with SSRIs, including fluoxetine, particularly when given in combination with other serotonergic and/or neuroleptic drugs. As these syndromes may result in potentially life-threatening conditions, treatment with Teva-Fluoxetine should be discontinued if such events (characterized by clusters of symptoms such as hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, mental status changes including confusion, irritability, extreme agitation progressing to delirium and coma) occur and supportive symptomatic treatment should be initiated. Due to the risk of serotonergic syndrome or neuroleptic malignant syndrome, Teva-Fluoxetine should not be used in combination with MAO inhibitors (including the antibiotic linezolid and the thiazine dye methylthioninium chloride (methylene blue) which are less well-known examples of MAOIs) or serotonin-precursors (such as L-tryptophan, oxitriptan) and should be used with caution in combination with other serotonergic drugs (triptans, certain tricyclic antidepressants, lithium, tramadol, St. John's Wort) due to the risk of serotonergic syndrome (see 2 CONTRAINDICATIONS and 9.4 Drug-Drug Interactions, Serotonergic Drugs).

Ophthalmologic

Angle-Closure Glaucoma

As with other antidepressants, fluoxetine can cause mydriasis, which may trigger an angle-closure attack in a patient with anatomically narrow ocular angles. Healthcare providers should inform patients to seek immediate medical assistance if they experience eye pain, changes in vision or swelling or redness in or around the eye.

Psychiatric

Suicide risk

The possibility of a 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.

Although a causal role for fluoxetine in inducing such events has not been established, an FDA analysis from pooled studies of antidepressants in psychiatric disorders found an increased risk for suicidal ideation and/or suicidal behaviors in pediatric and young adult (< 25 years of age) patients compared to placebo.

Close supervision of high-risk patients should accompany drug therapy and consideration should be given to the possible need for hospitalization. Health professionals should encourage patients of all ages to report any new or worsened distressing thoughts or feelings occurring at any time. In order to minimize the opportunity for overdosage, prescriptions for fluoxetine should be written for the smallest quantity of drug consistent with good patient management.

Because of the well established comorbidity between depression and other psychiatric disorders, the same precautions observed when treating patients with depression should be observed when treating patients with other psychiatric disorders (see 7 WARNINGS AND PRECAUTIONS, General, Potential Association with Behavioral and Emotional Changes, Including Self-Harm).

Activation of Mania/Hypomania

During premarketing clinical trials in a patient population comprised primarily of unipolar depressed patients, hypomania or mania occurred in approximately 1% of fluoxetine treated patients. The incidence in a general patient population which might also include bipolar depressives is unknown. The likelihood of hypomanic or manic episodes may be increased at the higher dosage levels. Such reactions require a reduction in dosage or discontinuation of the drug.

A major depressive episode may be the initial presentation of bipolar disorder. Patients with bipolar disorder may be at an increased risk of experiencing manic episodes when treated with antidepressants alone. Therefore, the decision to initiate symptomatic treatment of depression should only be made after patients have been adequately assessed to determine if they are at risk for bipolar disorder.

Electroconvulsive Therapy (ECT)

There are no clinical studies to support the safety and efficacy of combined use of ECT and fluoxetine. There have been rare reports of prolonged seizures in patients on fluoxetine receiving ECT treatment.

Renal

Severe Renal Impairment

Since fluoxetine is extensively metabolized, excretion of unchanged drug in urine is a minor route of elimination. However, until an adequate number of patients with severe renal impairment have been evaluated in the course of chronic treatment, fluoxetine should be used with caution in such patients.

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.

In two 6-week controlled studies in patients ≥ 60 years of age, 10 of 323 fluoxetine patients and 6 of 327 placebo recipients had a lowering of serum sodium below the reference range; this difference was not statistically significant. The lowest observed concentration of sodium in a fluoxetine treated patient was 129 mmol/L. The observed decreases were not clinically significant.

Reproductive Health: Female and Male Potential

- Fertility

  Male Fertility

  Animal data have shown that fluoxetine at levels in excess of the maximum tolerable dose may affect sperm quality (See 16 NON-CLINICAL TOXICOLOGY, General Toxicology, and Reproductive and Developmental Toxicology). In human case reports, some reversible changes in sperm quality have been reported with some SSRIs, including fluoxetine. An impact on human fertility has not been observed.

7.1 Special Populations

7.1.1 Pregnant Women

Pregnant Women and Newborns

There are no adequate and well-controlled clinical studies on the use of fluoxetine in pregnant women. Teva-Fluoxetine should not be administered to pregnant women or those intending to become pregnant unless in the opinion of the treating health professional, the expected benefits to the patient markedly outweigh the possible hazards to the fetus or the child.

See also: 4.2 Recommended Dose and Dosage Adjustment, Special Patient Populations; and, 7 WARNINGS AND PRECAUTIONS, General, Use of fluoxetine in Pregnant Women: Effects on Newborns sections.

Possible Risk of Cardiovascular Malformations following first trimester exposure to SSRIs

Results of a number of epidemiological studies of pregnancy outcomes following early maternal exposure to antidepressants have been inconsistent, with some finding no increased risk of malformations with fluoxetine exposure, while others have found a small increased risk for cardiovascular malformations (e.g., ventricular and septal defects) in infants with first trimester exposure to fluoxetine compared to those not exposed. The mechanism is unknown. Overall, the data suggest that the potential risk of having an infant with a cardiovascular malformation following maternal exposure to fluoxetine is less than 2/100 compared with an expected rate for such defects of approximately 1/100 in the general population. The use of Teva-Fluoxetine during pregnancy should be considered only if the potential benefit justifies the potential risk to the fetus taking into account the risks associated with untreated depression.

Complications following late third trimester exposure to SSRIs
Post-marketing reports indicate that some neonates exposed to fluoxetine, other SSRIs (selective serotonin reuptake inhibitors), or newer anti-depressants late in the third trimester have developed complications requiring prolonged hospitalization, respiratory support, and tube feeding. Such complications can arise immediately upon delivery. Reported clinical findings have included respiratory distress, cyanosis, apnea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycemia, hypotonia, hypertonia, hyperreflexia, tremor, jitteriness, irritability, and constant crying. These features are consistent with either a direct toxic effect of SSRIs and other newer anti-depressants or, possibly, a drug discontinuation syndrome. It should be noted that, in some cases, the clinical picture is consistent with serotonin syndrome (see 2 CONTRAINDICATIONS, Monoamine Oxidase Inhibitors).

Observational data suggests an increased risk (less than 2-fold) of postpartum hemorrhage following SSRI/SNRI exposure within a month of delivery, including fluoxetine (see 7 WARNINGS AND PRECAUTIONS, Hematologic, Abnormal Bleeding).

When treating a pregnant woman with Teva-Fluoxetine during the third trimester, the health professional should carefully consider the potential risks and benefits of treatment (see 4.2 Recommended Dose and Dosage Adjustment, Special Patient Populations section).

Risk of PPHN and exposure to SSRIs (including fluoxetine)
Exposure during late pregnancy to SSRIs, including fluoxetine, may have an increased risk for persistent pulmonary hypertension of the newborn (PPHN). PPHN occurs in 1-2 per 1,000 live births in the general population and is associated with substantial neonatal morbidity and mortality. In a retrospective case-control study of 377 women whose infants were born with PPHN and 836 women whose infants were born healthy, the risk for developing PPHN was approximately six-fold higher for infants exposed to SSRIs after the 20th week of gestation compared to infants who had not been exposed to antidepressants during pregnancy. A study of 831,324 infants born in Sweden in 1997-2005 found a PPHN risk ratio of 2.4 (95% CI 1.2-4.3) associated with patient-reported maternal use of SSRIs in “early pregnancy” and a PPHN risk ratio of 3.6 (95% CI 1.2-8.3) associated with a combination of patient-reported maternal use of SSRIs in “early pregnancy” and an antenatal SSRI prescription in “later pregnancy”.

7.1.2 Breast-feeding

Fluoxetine and its metabolites are excreted in breast milk, and have been observed to reach high levels in the plasma of nursing infants. Women who are taking Teva-Fluoxetine should not breast feed unless, in the opinion of the treating health professional, breast feeding is necessary, in which case the infant should be closely monitored.

In one breast milk sample, the concentration of fluoxetine plus norfluoxetine was 70.4 ng/mL. The concentration in the mother's plasma was 295.0 ng/mL. No adverse effects on the infant were reported. In another case, a 6-week infant, nursed by a mother on fluoxetine, developed crying, decreased sleep, vomiting and watery stools. The breast milk showed concentrations of

69 ng/mL for fluoxetine and 90 ng/mL for norfluoxetine. In the infant's plasma, the concentrations of fluoxetine and norfluoxetine on the second day of feeding were 340 and 208 ng/mL, respectively.

7.1.3 Pediatrics

Pediatrics (< 18 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use. See 7 WARNINGS AND PRECAUTIONS, General, Potential Association with Behavioural and Emotional Changes, including Self-Harm. See also 8.2.1 Clinical Trial Adverse Reactions – Pediatrics, Potential for Effects on Growth in Pediatric Patients.

7.1.4 Geriatrics

Geriatrics (≥ 60 years of age): Evaluation of patients over the age of 60 who received fluoxetine 20 mg daily revealed no unusual pattern of adverse events relative to the clinical experience in younger patients. These data are however insufficient to rule out possible age-related differences during chronic use, particularly in elderly patients who have concomitant systemic illnesses or who are receiving concomitant drugs. See 1 INDICATIONS, and 4.2 Recommended Dose and Dosage Adjustment, Special Patient Populations sections.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

Commonly Observed Adverse Events

In clinical trials, the most commonly observed adverse events associated with the use of fluoxetine and not seen at an equivalent incidence among placebo treated patients were: central nervous system complaints, including headache, nervousness, insomnia, drowsiness, fatigue or asthenia, anxiety, tremor, and dizziness or lightheadedness; gastrointestinal complaints, including nausea, diarrhea, dry mouth and anorexia; and excessive sweating.

Adverse Events Leading to Discontinuation of Treatment

Fifteen percent of approximately 4,000 patients who received fluoxetine in North American clinical trials discontinued treatment due to an adverse event. The more common events causing discontinuation from depression trials in adults and elderly, included: psychiatric, primarily nervousness, anxiety, and insomnia; digestive, primarily nausea; nervous system, primarily dizziness, asthenia, and headaches; skin, primarily rash and pruritus.

In obsessive compulsive disorder studies, 12.1% of fluoxetine treated patients discontinued treatment early because of adverse events. Anxiety and rash, at incidences of less than 2%, were the most frequently reported events. In bulimia nervosa studies, 10.2% of fluoxetine treated patients discontinued treatment early because of adverse events. Insomnia, anxiety and rash, at incidences of less than 2%, were the most frequently reported events.

Adverse Events Subsequent to Discontinuation
Symptoms associated with discontinuation of fluoxetine have been reported in clinical trials and post-marketing (e.g., headache, insomnia, paresthesias, nervousness, anxiety, nausea, sweating, numbness, dizziness, jitteriness, asthenia, or other symptoms which may be of clinical significance). The majority of these are mild and self–limiting. Fluoxetine has been only rarely associated with such symptoms. Plasma fluoxetine and norfluoxetine concentrations decrease gradually at the conclusion of therapy, which makes dose tapering unnecessary in most patients. See 4.1 Dosing Considerations, Discontinuation of Treatment; and 7 WARNINGS AND PRECAUTIONS, General.

Serious Adverse Reactions
Suicidal thoughts and acts are far more common among depressed patients than in the general population. It is estimated that suicide is 22 to 36 times more prevalent in depressed persons than in the general population. A comprehensive meta-analysis of pooled data from 17 double blind clinical trials in patients with major depressive disorder compared fluoxetine (n = 1765) with a tricyclic antidepressant (n = 731) or placebo (n = 569), or both. The pooled incidence of emergence of substantial suicidal ideation was 1.2% for fluoxetine, 2.6% for placebo, and 3.6% for tricyclic antidepressants.

In countries where the drug has already been marketed, the following potentially serious adverse reactions have been reported; interactions with MAO inhibitors and possibly other drugs, allergic reactions, cardiovascular reactions, syndrome of inappropriate ADH secretion, and grand mal seizure. Death and life-threatening events have been associated with some of these reactions, although causal relationship to fluoxetine has not necessarily been established.

Post-marketing experience also confirms the profile of adverse reactions commonly reported during clinical trials with fluoxetine including allergic skin reactions.

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse drug reaction rates observed in the clinical trials; therefore may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

Multiple doses of fluoxetine had been administered to 10,782 patients with various diagnoses in US clinical trials as of May 8, 1995. Adverse events were recorded by clinical investigators using descriptive terminology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse events without first grouping similar types of events into a limited (i.e., reduced) number of standardized event categories.

Adults:

In the tables and tabulations that follow, COSTART Dictionary terminology has been used to classify reported adverse events. The stated frequencies represent the proportion of individuals who experienced, at least once, a treatment-emergent adverse event of the type listed. An event was considered treatment-emergent if it occurred for the first time or worsened while receiving therapy following baseline evaluation. It is important to emphasize that events reported during therapy were not necessarily caused by it.

The prescriber should be aware that the figures in the tables and tabulations cannot be used to predict the incidence of side effects in the course of usual medical practice where patient characteristics and other factors differ from those that prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses, and investigators. The cited figures, however, do provide the prescribing health professional with some basis for estimating the relative contribution of drug and nondrug factors to the side effect incidence rate in the population studied.

Table 2: Treatment-Emergent Adverse Events Incidence in Fluoxetine versus Placebo Trials Listed by Indication

Percentage of Patients Reporting Event								
Body System/ Adverse Event	**DEPRESSION* (Adults)**		**DEPRESSION (Elderly)**		**OCD***		**BULIMIA ***	
	Fluoxetine (N=1728)	**Placebo (N=975)**	**Fluoxetine (N=335)**	**Placebo (N=336)**	**Fluoxetine (N=266)**	**Placebo (N=89)**	**Fluoxetine (N=450)**	**Placebo (N=267)**
Nervous System								
Headache	--	--	28	24	--	--	--	--
Nervousness	14	9	12	7	14	15	11	5
Insomnia	16	9	18	12	28	22	33	13
Somnolence	13	6	9	6	17	7	13	5
Anxiety	12	7	13	8	14	7	15	9
Tremor	10	3	8	4	9	1	13	1
Dizziness	--	--	11	10	--	--	--	--
Libido, decreased	3	0	--	--	11	2	5	1
Abnormal dreams	1	1	--	--	5	2	5	3
Digestive System								
Nausea	21		17	7	26	13	29	11
Diarrhea	9		14	9	--	--	--	--
Dry Mouth	--	--	7	5	12	3	9	6
Anorexia	10	7	11	2	17	10	8	4
Dyspepsia	11	2	11	5	10	4	10	6

Constipation	7	5	7	6	--	--	--	--
Flatulence	--	--	7	2	--	--	--	--
	--	--						
Skin and Appendages	8	3	7	3	7	0	8	3
Sweating	4	3	--	--	6	3	4	4
Rash								
Body as a Whole								
Asthenia	9	5	13	10	15	11	21	9
Flu syndrome	3	4	--	--	10	7	8	3
Back Pain	--	--	7	9	--	--	--	--
Abdominal Pain	--	--	6	6	--	--	--	--
Myalgia	--	--	3	5	--	--	--	--
Respiratory System	--	--	9	14	--	--	--	--
Rhinitis	3	3	--	--	11	9	10	5
Pharyngitis	1	4	3	7	5	2	6	4
Sinusitis	--	--	--	--	7	--	11	--
Yawn								
Cardiovascular System								
Vasodilatation	3	2	--	--	5	0	2	1
Urogenital System								
Abnormal	--	--	--	--	7	--	7	--
Ejaculation †	2	--	--	--	--	--	7	--
Impotence †								

† Denominator used was for males only (N= 690 fluoxetine depression; N=410 placebo depression; N=116 fluoxetine OCD ; N=43 placebo OCD; N=14 fluoxetine bulimia; N=1 placebo bulimia).

-- Incidence less than 1%

* The most common treatment-emergent adverse events associated with the use of fluoxetine (incidence of at least 5% for fluoxetine and at least twice that for placebo within at least one of the indications) for the treatment of depression, OCD, and bulimia in US controlled clinical trials.

Table 3 enumerates treatment-emergent adverse events that occurred in 2% or more patients treated with fluoxetine and with incidence greater than placebo who participated in US controlled clinical trials comparing fluoxetine with placebo in the treatment of depression, OCD, or bulimia. Table 3 provides combined data for the pool of studies that are provided separately by indication in Table 2.

Table 3: Combined Treatment-Emergent Adverse Events Incidence for Patients Treated with fluoxetine versus Placebo

Percentage of patients reporting event		
	Depression, OCD, and bulimia combined	
Body System/Adverse Event *	**Fluoxetine (N=2444)**	**Placebo (N=1331)**
Body as a Whole		
Headache	21	20
Asthenia	12	6
Flu syndrome	5	4
Fever	2	1
Cardiovascular System		
Vasodilatation	3	1
Palpitation	2	1
Digestive System		
Nausea	23	10
Diarrhea	12	8
Anorexia	11	3
Dry mouth	10	7
Dyspepsia	8	5
Flatulence	3	2
Vomiting	3	2
Metabolic and Nutritional Disorders		
Weight loss	2	1
Nervous System		
Insomnia	20	11
Anxiety	13	8
Nervousness	13	9
Somnolence	13	6
Dizziness	10	7
Tremor	10	3
Libido decreased	4	--
Respiratory System		
Pharyngitis	5	4
Yawn	3	--
Skin and Appendages		
Sweating	8	3
Rash	4	3
Pruritus	3	2
Special Senses		
Abnormal vision	3	1

* Included are events reported by at least 2% of patients taking fluoxetine, except the following events, which had an incidence on placebo > fluoxetine (depression, OCD, and bulimia combined): abdominal pain, abnormal dreams, accidental injury, back pain, chest pain, constipation, cough increased, depression (includes suicidal thoughts), dysmenorrhea, gastrointestinal disorder, infection, myalgia, pain, paresthesia, rhinitis, sinusitus, thinking abnormal.
- Incidence less than 1%.

Table 4 lists the adverse events associated with discontinuation of fluoxetine treatment (incidence at least twice that for placebo and at least 1% for fluoxetine in clinical trials collecting only a primary event associated with discontinuation) in depression, OCD, and bulimia. For symptoms associated with discontinuation of fluoxetine in clinical trials and post-marketing, see 8.5 Post-Market Adverse Reactions section.

Table 4: Adverse Events Associated with Discontinuation of fluoxetine Treatment

Depression, OCD, and Bulimia Combined (N=1108)	Depression (N=392)	OCD (N=266)	Bulimia (N=450)
--	--	Anxiety (2%)	--
Insomnia (1%)	--	--	Insomnia (2%)
--	Nervousness (1%)	--	--
--	--	Rash (1%)	--

Male and Female Sexual Dysfunction with SSRIs:
Although changes in sexual desire, sexual performance, and sexual satisfaction often occur as manifestations of a psychiatric disorder, they may also be a consequence of pharmacologic treatment. In particular, some evidence suggests that SSRIs can cause such untoward sexual experiences.

Reliable estimates of the incidence and severity of untoward experiences involving sexual desire, performance, and satisfaction are difficult to obtain, however, in part because patients and health professionals may be reluctant to discuss them. Accordingly, estimates of the incidence of untoward sexual experience and performance, cited in product labeling, are likely to underestimate their actual incidence. In patients enrolled in depression, OCD, and bulimia placebo-controlled clinical trials, decreased libido was the only sexual side effect reported by at least 2% of patients taking fluoxetine (4% fluoxetine, < 1% placebo). There have been spontaneous reports in women taking fluoxetine of orgasmic dysfunction, including anorgasmia.

There are no adequate and well-controlled studies examining sexual dysfunction with fluoxetine treatment. Symptoms of sexual dysfunction occasionally persisting after discontinuation of fluoxetine treatment have been observed in spontaneous reports. Priapism

has been reported with all SSRIs. While it is difficult to know the precise risk of sexual dysfunction associated with the use of SSRIs, health professionals should routinely inquire about such possible side effects.

Other Frequent Treatment Emergent Adverse Events
The following is a list of additional treatment emergent adverse events reported frequently (i.e., occurring on 1 or more occasions in at least 1/100 patients) at any time by individuals taking fluoxetine in US clinical trials (10, 782 patients):

Body as a Whole: chills

Cardiovascular system: hemorrhage, hypertension

Digestive system: increased appetite, nausea and vomiting
Metabolic and Nutritional: weight gain

Nervous System: abnormal movement/tremor1, agitation, amnesia, confusion, emotional lability, fatigue[2], headache, sleep abnormalities[3]

Special Senses: ear pain, taste perversion, tinnitus

Urogenital System: gynaecological bleeding[*], sexual dysfunction[*,4] urinary frequency

8.2.1 Clinical Trial Adverse Reactions – Pediatrics

Pediatrics (< 18 years of age):
Frequent: epistaxis

Potential for Effects on Growth in Pediatric Patients:
Fluoxetine is not indicated for use in patients below the age of 18 years (see WARNINGS AND PRECAUTIONS, General, Potential Association with Behavioural and Emotional Changes, including Self-Harm**).**
Decreased weight gain and a lesser gain in height have been observed in association with the use of fluoxetine in children and adolescent patients. After 19 weeks of treatment in a clinical trial, pediatric subjects treated with fluoxetine (n = 88) were recorded as gaining an average of 1.1 cm less in height than subjects treated with placebo (n = 75). However, the study was not designed for a rigorous assessment of growth (e.g., heights were recorded to the nearest rounded inch), and thus a definite interpretation of this finding was compromised. This is exemplified by the reported outcome of a loss in height for 17 of the patients. Notwithstanding these limitations, an attenuation of height gain with acute fluoxetine treatment cannot be excluded. (See also 16 NON-CLINICAL TOXICOLOGY, Juvenile Toxicity). Fluoxetine treatment was also associated with a decrease in serum alkaline phosphatase levels in this study. Limited evidence is available concerning the longer-term effects of fluoxetine on the development and

maturation of children and adolescent patients. Height and weight should be monitored periodically in pediatric patients receiving fluoxetine.

8.3 Less Common Clinical Trial Adverse Reactions

Treatment-Emergent Adverse Events
Following is a list of all treatment-emergent adverse events reported at anytime by individuals taking fluoxetine in US clinical trials (10,782 patients) except: (1) those listed in the body or footnotes of Tables 2 or 3 above or elsewhere in labelling; (2) those for which the COSTART terms were uninformative or misleading; (3) those events for which a causal relationship to fluoxetine use was considered remote; and (4) events occurring in only 1 patient treated with fluoxetine and which did not have a substantial probability of being acutely life-threatening.

Events are further classified within body system categories and enumerated in order of decreasing frequency using the following definitions: infrequent adverse events are those occurring in less than 1/100 but at least 1/1,000 patients; rare events are those occurring in less than 1/1,000 patients.

Body as a Whole
Infrequent: chills and fever, face edema, feeling abnormal, intentional overdose, malaise, pelvic pain, suicide attempt.
Rare: abdominal syndrome acute, hypothermia, intentional injury, neuroleptic malignant syndrome‡, photosensitivity reaction.
*characterized by the clustering of clinical features of changes in mental state and neuromuscular activity, in combination with autonomic nervous system dysfunction.

Cardiovascular System
Infrequent: angina pectoris, arrhythmia, congestive heart failure, hypotension, migraine, myocardial infarct, postural hypotension, syncope, tachycardia, vascular headache.
Rare: atrial fibrillation, bradycardia, cerebral embolism, cerebral ischemia, cerebrovascular accident, extrasystoles, heart arrest, heart block, pallor, peripheral vascular disorder, phlebitis, shock, thrombophlebitis, thrombosis, vasospasm, ventricular arrhythmia, ventricular extrasystoles, ventricular fibrillation.

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[1] COSTART group term **abnormal movement/tremor** includes the independent terms: *frequent*: tremor; *infrequent*: ataxia, buccoglossal, myoclonus; *rare*: twitching.
[2] COSTART group term **fatigue** includes the independent terms: *frequent*: asthenia, somnolence.
[3] COSTART group term **sleep abnormalities** includes the independent terms: *frequent*: insomnia; *rare*: abnormal dreams.

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* Adjusted for gender
[4] COSTART group term **sexual dysfunction** includes the independent terms: *frequent*: impotence, libido decreased; *infrequent*: anorgasmia, delayed or absent ejaculation.
‡ Neuroleptic malignant syndrome is the COSTART term which best captures serotonin syndrome.
† Personality disorder is the COSTART term for designating non-aggressive objectionable behavior.

Digestive System
***Infrequent*:** aphthous stomatitis, cholelithiasis, colitis, dysphagia, eructation, esophagitis, gastritis, gastroenteritis, glossitis, gum hemorrhage, hyperchlorhydria, increased salivation, liver function tests abnormal, melena, mouth ulceration, nausea/vomiting/diarrhea, stomach ulcer, stomatitis, thirst.

***Rare*:** biliary pain, bloody diarrhea, cholecystitis, duodenal ulcer, enteritis, esophageal ulcer, fecal incontinence, gastrointestinal hemorrhage, hematemesis, hemorrhage of colon, hepatitis, intestinal obstruction, liver fatty deposit, oesophageal pain, pancreatitis, peptic ulcer, rectal hemorrhage, salivary gland enlargement, stomach ulcer hemorrhage, tongue edema.

Endocrine System
***Infrequent*:** hypothyroidism
***Rare*:** diabetic acidosis, diabetes mellitus.

Hemic and Lymphatic System
***Infrequent*:** anemia, ecchymosis.
***Rare*:** blood dyscrasia, hypochromic anemia, leukopenia, lymphedema, lymphocytosis, petechia,
purpura, thrombocythemia, thrombocytopenia.

Metabolic and Nutritional
Infrequent: dehydration, generalized edema, gout, hypercholesteremia, hyperlipemia, hypokalemia, peripheral edema.
Rare: alcohol intolerance, alkaline phosphatase increased, BUN increased, creatine phosphokinase increased, hyperkalemia, hyperuricemia, hypocalcemia, iron deficiency anemia, SGPT increased.

Musculoskeletal System
***Infrequent*:** arthritis, bone pain, bursitis, leg cramps, tenosynovitis.
***Rare*:** arthrosis, chondrodystrophy, myasthenia, myopathy, myositis, osteomyelitis, osteoporosis, rheumatoid arthritis.

Nervous System
Infrequent: abnormal gait, acute brain syndrome, akathisia, apathy, balance disorder, bruxism, CNS depression, CNS stimulation, depersonalization, euphoria, hallucinations, hostility,

hyperkinesia, hypertonia, hypesthesia, incoordination, libido increased, neuralgia, neuropathy, neurosis, paranoid reaction, personality disorder[†], psychosis, vertigo.
Rare: abnormal electroencephalogram, antisocial reaction, circumoral paresthesia, coma, delusions, dysarthria, dystonia, extrapyramidal syndrome, foot drop, hyperesthesia, neuritis, paralysis, reflexes decreased, reflexes increased, stupor.

[†] Personality disorder is the COSTART term for designating non-aggressive objectionable behavior.

Respiratory System
Infrequent: asthma, epistaxis, hiccup, hyperventilation.
Rare: apnea, atelectasis, cough decreased, emphysema, hemoptysis, hypoventilation, hypoxia, larynx edema, lung edema, pneumothorax, stridor.

Skin and Appendages
Infrequent: acne, alopecia, contact dermatitis, eczema, maculopapular rash, skin discoloration, skin ulcer, vesiculobullous rash.
Rare: furunculosis, herpes zoster, hirsutism, petechial rash, psoriasis, purpuric rash, pustular rash, seborrhea.

Special Senses
Infrequent: conjunctivitis, dry eyes, mydriasis, photophobia.
Rare: blepharitis, deafness, diplopia, exophthalmos, eye hemorrhage, glaucoma, hyperacusis, iritis, parosmia, scleritis, strabismus, taste loss, visual field defect.

Urogenital System
Infrequent: abortion*, albuminuria, amenorrhea*, breast enlargement, breast pain, cystitis, dysuria, female lactation*, fibrocystic breast*, hematuria, leukorrhea*, menorrhagia*, metrorrhagia*, nocturia, polyuria, urinary incontinence, urinary retention, urinary urgency.
Rare: breast engorgement, glycosuria, hypomenorrhea*, kidney pain, oliguria, priapism*, uterine fibroids enlarged*.

[*] Adjusted for gender.

8.4 Abnormal laboratory findings

ECG Findings*:*
In a placebo-controlled clinical trial in major depressive disorder, fluoxetine titrated to doses in the range of 40-80 mg/day was associated with a statistically significant placebo-adjusted mean change from baseline in the Fridericia-corrected QT interval (QTcF=QT/RR0.33) of 8.6 ms (90%

CI 4.5, 12.6). See 7 WARNINGS AND PRECAUTIONS, Cardiovascular; 9.4 Drug-Drug Interactions, QTc-Prolonging Drugs; 10.2 Pharmacodynamics, Electrocardiography

8.5 Post-Market Adverse Reactions

Voluntary reports of adverse events temporally associated with fluoxetine that have been received since market introduction and that may have no causal relationship with the drug include the following: aplastic anemia, atrial fibrillation, bone fractures, cardiac arrest, cataract, cerebral vascular accident, cholestatic jaundice, confusion, dyskinesia (including, for example, a case of buccal-lingual-masticatory syndrome with involuntary tongue protrusion reported to develop in a 77-year-old female after 5 weeks of fluoxetine therapy and which completely resolved over the next few months following drug discontinuation), eosinophilic pneumonia, epidermal necrolysis, erythema multiforme, erythema nodosum, exfoliative dermatitis, gastrointestinal bleeding[5], galactorrhea, gynecomastia, heart arrest, hepatic failure/necrosis, hyperprolactinemia, hypoglycemia, immune-related hemolytic anemia, kidney failure, memory impairment, misuse/abuse, movement disorders developing in patients with risk factors including drugs associated with such events and worsening of preexisting movement disorders, neuroleptic malignant syndrome-like events, optic neuritis, pancreatitis, pancytopenia, priapism, pulmonary embolism, pulmonary hypertension, QT prolongation, serotonin syndrome (a range of signs and symptoms that can rarely, in most severe cases, resemble neuroleptic malignant syndrome), Stevens-Johnson syndrome, sudden unexpected death, suicidal ideation, thrombocytopenia, thrombocytopenic purpura, vaginal bleeding after drug withdrawal, ventricular tachycardia (including torsades de pointes-type arrhythmias and ventricular fibrillation) and violent behaviours.

[5]Includes: esophageal varices hemorrhage, gingival and mouth bleeding, hematemesis, hematochezia, hematomas [intraabdominal, peritoneal], hemorrhage [anal, esophageal, gastric, gastrointestinal (upper and lower), haemorrhoidal, peritoneal, rectal], hemorrhagic diarrhoea and enterocolitis, hemorrhagic diverticulitis, hemorrhagic gastritis, melaena, and ulcer hemorrhage [esophageal, gastric, duodenal].

9 DRUG INTERACTIONS

9.1 Serious Drug Interactions

Serious Drug Interactions

- **Monoamine Oxidase Inhibitors: See 2 CONTRAINDICATIONS and 9.4 Drug-Drug Interactions**
- **Thioridazine: See 2 CONTRAINDICATIONS and 9.4 Drug-Drug Interactions**

9.2 Drug Interactions Overview

Fluoxetine, like some other agents that are metabolized by the P4502D6 system, inhibits the activity of this isoenzyme. Therefore, co-therapy with medications that are predominantly metabolized by the P4502D6 system and that have a relatively narrow therapeutic index (e.g. flecainide, encainide, vinblastine, carbamazepine and tricyclic antidepressants) 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 5 weeks. If fluoxetine is added to the treatment regimen of a patient already receiving a drug metabolized by P4502D6, the need for decreased dose of the original medication should be considered. The aforementioned drugs with a narrow therapeutic index represent the greatest concern.

Other drugs that have demonstrated increased plasma values or magnified effects when co-administered with fluoxetine include: phenytoin, antipsychotics, benzodiazapines, thioridazine (see 2 CONTRAINDICATIONS), St. John's Wort and warfarin.

As fluoxetine is highly bound to plasma proteins, co-administration with another drug which is also highly bound (e.g., warfarin, digitoxin) may result in adverse effects due to an increase in plasma levels of either unbound drug.

There are little data available on the concomitant use of fluoxetine and alcohol.

9.3 Drug-Behavioural Interactions

Alcohol: The concomitant use of fluoxetine and alcohol on cognitive and psychomotor effects in depressed, panic disorder or OCD patients is not known and is not recommended. Interaction with lifestyle interactions have not been established.

9.4 Drug-Drug Interactions

QTc-Prolonging Drugs*:* Pharmacokinetic and pharmacodynamic studies of fluoxetine combined with other medicinal products that prolong the QT interval have not been performed. An additive effect of fluoxetine and these medicinal products cannot be excluded. Therefore, co-administration of fluoxetine with medicinal products that have a clear QT interval prolonging effect is discouraged. Drugs that have been associated with QTc interval prolongation and/or torsade de pointes include, but are not limited to, the examples in the following list. Chemical/pharmacological classes are listed if some, although not necessarily all, class members have been implicated in QTc prolongation and/or torsade de pointes:

- Class IA antiarrhythmics (e.g., quinidine, procainamide, disopyramide)
- Class III antiarrhythmics (e.g., amiodarone, sotalol, ibutilide, dronedarone)
- Class 1C antiarrhythmics (e.g., flecainide, propafenone)
- antipsychotics (e.g., chlorpromazine, pimozide, haloperidol, droperidol, ziprasidone)
- antidepressants (e.g., citalopram, venlafaxine, tricyclic/tetracyclic antidepressants e.g., amitriptyline, imipramine, maprotiline)

- opioids (e.g., methadone)
- macrolide antibiotics and analogues (e.g., erythromycin, clarithromycin, telithromycin, tacrolimus)
- quinolone antibiotics (e.g., moxifloxacin, levofloxacin, ciprofloxacin)
- antimalarials (e.g., quinine, chloroquine)
- azole antifungals (e.g., ketoconazole, fluconazole, voriconazole)
- domperidone
- 5-HT3 receptor antagonists (e.g., dolasetron, ondansetron)
- tyrosine kinase inhibitors (e.g., vandetanib, sunitinib, nilotinib, lapatinib)
- histone deacetylase inhibitors (e.g., vorinostat)
- beta-2 adrenoceptor agonists (e.g., salmeterol, formoterol).

Drugs that Affect Electrolytes: The concomitant use of fluoxetine with drugs that can disrupt electrolyte levels is discouraged. Drugs that decrease electrolyte levels include, but are not limited to, the following: loop, thiazide, and related diuretics; laxatives and enemas; amphotericin B; high dose corticosteroids.

The above lists of potentially interacting drugs are not comprehensive. (See also 7 WARNINGS AND PRECAUTIONS, Cardiovascular; 8.4 Abnormal laboratory findings & 8.5 Post-Market Adverse Reactions; 10.2 Pharmacodynamics, Electrocardiography).

Monoamine Oxidase Inhibitors*:* Combined use of Teva-Fluoxetine and MAO inhibitors (including the antibiotic linezolid and the thiazine dye methylthioninium chloride (methylene blue) which are less well-known examples of MAOIs) is contraindicated due to the potential for serious reactions with features resembling serotonin syndrome or neuroleptic malignant syndrome (See 2 CONTRAINDICATIONS; 7 WARNINGS AND PRECAUTIONS, Serotonin Syndrome/Neuroleptic Malignant Syndrome).

Thioridazine*:* Potential Interactions with Thioridazine (see also 2 CONTRAINDICATIONS): In a study of 19 healthy male subjects, which included 6 slow and 13 rapid hydroxylators of debrisoquin, a single 25 mg oral dose of thioridazine produced a 2.4-fold higher Cmax and a 4.5-fold higher AUC for thioridazine in the slow hydroxylators compared to the rapid hydroxylators. The rate of debrisoquin hydroxylation is felt to depend on the level of cytochrome P4502D6 isozyme activity. Thus, this study suggests that drugs which inhibit P4502D6, such as certain SSRIs, including fluoxetine, will produce elevated plasma levels of 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. Due to the risk of serious ventricular arrhythmias and sudden death potentially associated with elevated plasma levels of thioridazine, thioridazine should not be concomitantly administered, nor within a minimum of 5 weeks after fluoxetine has been

discontinued, nor should fluoxetine be administered within 2 weeks after thioridazine has been discontinued (see 2 CONTRAINDICATIONS).

Drugs Affecting Platelet Function (e.g., NSAIDS, ASA and other anticoagulants)*:* Serotonin release by platelets plays an important role in hemostasis. Epidemiological studies of the case-control and cohort design that have demonstrated an association between use of psychotropic drugs that interfere with serotonin reuptake and the occurrence of upper gastrointestinal bleeding have also shown that concurrent use of an NSAID, ASA or other anticoagulants may potentiate the risk of bleeding.

Altered anticoagulant effects, including increased bleeding, have been reported when SSRIs or SNRIs are coadministered with warfarin. Patients receiving warfarin therapy should be carefully monitored when fluoxetine is initiated or discontinued [see 7 WARNINGS AND PRECAUTIONS, Hematologic, Abnormal Bleeding].

Drugs Tightly Bound to Plasma Protein: Because fluoxetine is highly bound to plasma protein, the administration of fluoxetine to a patient taking another drug which is tightly bound to protein (e.g., warfarin, 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.

Drugs Metabolized by P4502D6 Isoenzyme*:* Approximately 3 to 10% of the normal population has a genetic defect that leads to reduced levels of activity of the cytochrome P450 isoenzyme P4502D6. Such individuals have been referred to as "poor metabolizers" of drugs such as debrisoquine, dextrometorphan, sparteine, tricyclic antidepressants (e.g., nortryptiline, amitriptyline, imipramine, and desipramine), phenothiazine neuroleptics (e.g., perphenazine and thioridazine) and Type 1C antiarrhythmics (e.g., propafenone and flecainide).

Conversely, approximately 90 to 97% of the normal population do not have this genetic defect, and are known as "extensive metabolizers". Fluoxetine, like other agents that are metabolized by the P4502D6 system, inhibits the activity of this iso enzyme, and thus may make normal "extensive" metabolizers resemble "poor metabolizers". Therapy with medications that are predominantly metabolized by the P4502D6 system and that have a relatively narrow therapeutic index (e.g., flecainide, encainida, vinblastine, carbamazepine and tricyclic antidepressants) 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 5 weeks.

If fluoxetine is added to the treatment regimen of a patient already receiving a drug metabolized by P4502D6 the need for decreased dose of the original medication should be considered. The aforementioned drugs with a narrow therapeutic index represent the gre atest concern.

Tamoxifen: Pharmacokinetic interaction between CYP2D6 inhibitors and tamoxifen, showing a 65-75% reduction in plasma levels of one of the more active forms of the tamoxifen, i.e.,

endoxifen, has been reported in the literature. Reduced efficacy of tamoxifen has been reported with concomitant usage of some SSRI antidepressants in some studies. As a reduced effect of tamoxifen cannot be excluded, co-administration with potent CYP2D6 inhibitors (including fluoxetine) should whenever possible be avoided (see 7 WARNINGS AND PRECAUTIONS).

Impact of CYP2D6 Inhibition on Fluoxetine Metabolism: Both the pharmacokinetic properties and relative proportion of metabolites of fluoxetine may be affected by a patient's CYP2D6 pharmacogenetic phenotype, or by a number of different drugs known to inhibit the CYP2D6 enzyme.

Drugs Metabolized by Cytochrome P4503A4: In an *in vivo* interaction study involving co-administration of fluoxetine with single doses of terfenadine (a cytochrome P4503A4 substrate), no increase in plasma terfenadine concentrations occurred with concomitant fluoxetine. In addition, *in vitro* studies have shown ketoconazole, a potent inhibitor of P4503A4 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 P4503A4 activity is not likely to be of clinical significance.

Tricyclic Antidepressants: In two studies, previously stable plasma levels of imipramine and desipramine have increased greater than 2 to 10-fold when fluoxetine has been administered in combination. This influence may persist for three weeks or longer after fluoxetine is discontinued. Thus, the dose of tricyclic antidepressant (TCA) may need to be reduced and plasma TCA concentrations may need to be monitored temporarily when fluoxetine is coadministered or has been recently discontinued. See 7 WARNINGS AND PRECAUTIONS; and 10.3 Pharmacokinetics, Accumulation and Slow Elimination sections.

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.

Tryptophan: Five patients receiving fluoxetine in combination with tryptophan experienced adverse reactions, including agitation, restlessness and gastrointestinal distress.

Benzodiazepines: 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 alprazolam levels. Consideration should be given to monitoring of clinical status. Experience with the use of fluoxetine in combination with other CNS-active drugs is limited and caution is advised if such concomitant medication is required.

Antipsychotics: Elevation of blood levels of haloperidol and clozapine and in some cases, clinical manifestations of toxicity have been observed with coadministration of fluoxetine. Consideration should be given to monitoring of clinical status.

Serotonergic Drugs*:* Based on the mechanism of action of fluoxetine and the potential for serotonin syndrome, caution is advised when fluoxetine is coadministered with other drugs or agents that may affect the serotonergic neurotransmitter systems, such as tryptophan, triptans, serotonin reuptake inhibitors, linezolid (an antibiotic which is a reversible non-selective MAOI), lithium, tramadol, fentanyl and its analogues, dextromethorphan, tapentadol, meperidine, methadone, pentazocine or St. John's Wort (see 7 WARNINGS AND PRECAUTIONS, Serotonin Syndrome/Neuroleptic Malignant Syndrome).

Triptans (5HT1 agonists): There have been rare postmarketing reports describing patients with weakness, hyperreflexia, and incoordination following the use of a selective serotonin reuptake inhibitor (SSRI) and the 5HT1 agonist, sumatriptan. If concomitant treatment with triptan and an SSRI (e.g., fluoxetine, fluvoxamine, paroxetine, sertraline, or citalopram) is clinically warranted, appropriate observation of the patient is advised. The possibility of such interactions should also be considered if other 5HT1 agonists are to be used in combination with SSRIs (see 7 WARNINGS AND PRECAUTIONS, Serotonin Syndrome/Neuroleptic Malignant Syndrome).

Phenytoin: In patients on stable, maintenance doses of phenytoin, plasma phenytoin concentrations increased substantially and symptoms of phenytoin toxicity appeared (nystagmus, diplopia, ataxia and CNS depression) following initiation of concomitant fluoxetine treatment.

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. Consideration should be given to monitoring of clinical status when fluoxetine treatment is initiated in these patients.

9.5 Drug-Food Interactions

Absorption of fluoxetine is not affected by food.

9.6 Drug-Herb Interactions

St. John's Wort*:* In common with other SSRI's, pharmacodynamic interactions between fluoxetine and the herbal remedy St. John's Wort may occur and may result in an increase in undesirable effects.

9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

The mechanism of fluoxetine is unknown. The antidepressant, antiobsessional, and antibulimic actions of fluoxetine are presumed to be linked to its ability to selectively inhibit the neuronal reuptake of serotonin. At clinically relevant doses fluoxetine blocks the uptake of serotonin into human platelets.

10.2 Pharmacodynamics

Antagonism of muscarinic, histaminergic and α_1- adrenergic receptors has been hypothesized to be associated with various anticholinergic, sedative and cardiovascular effects of classical tricyclic antidepressant drugs. *In vitro* receptor binding studies have demonstrated that fluoxetine binds to these and other membrane receptors [opiate, serotonergic (5-HT_1, 5-HT_2), adrenergic
(α_1, α_2, β) and dopaminergic] much less potently than do the tricyclic drugs.

Electrocardiography:
A double-blind, placebo-controlled, randomised, multiple dose study was performed in two cohorts of healthy adult subjects (CYP2D6 intermediate and extensive metabolizers). In the first cohort, subjects received once-daily oral dosing for 28 days with fluoxetine 20 mg (N = 12) or placebo (N = 4), whilst in the second cohort, subjects received once-daily oral dosing for 28 days with fluoxetine 40 mg (N = 12) or placebo (N = 4). Serial ECG assessments were performed at baseline and on days 1 and 28 of treatment. For the 40 mg fluoxetine treatment (N = 12), the maximal mean difference from placebo in change from time-averaged baseline in QTcF ($QT/RR^{0.33}$) was 12.005 msec (90% CI 4.412, 19.598) on day 28. For the 20-mg treatment, the corresponding placebo-adjusted increase in the QTcF interval was 4.841 msec (90% CI -4.009, 13.69) (see 7 WARNINGS AND PRECAUTIONS, Cardiovascular; 8.2 Clinical Trial Adverse Reactions, ECG Findings & 8.5 Post-Market Adverse Reactions; 9 DRUG INTERACTIONS).

10.3 Pharmacokinetics

Absorption, Distribution, Metabolism, and Excretion:
Fluoxetine is well absorbed after oral administration. In man, 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 inconsequentially. Thus, fluoxetine may be administered with or without food.

Fluoxetine is extensively metabolized in the liver to norfluoxetine, and other unidentified metabolites. The pharmacological activity of norfluoxetine, which is formed by demethylation of fluoxetine appears to be similar to that of the parent drug. Norfluoxetine contributes to the long duration of action of fluoxetine. The primary route of elimination appears to be hepatic metabolism to inactive metabolites excreted by the kidney. The elimination half-life of fluoxetine is 4 to 6 days and that of its active metabolite is 4 to 16 days.

Clinical Issues Related to Metabolism/Elimination:

Variability in Metabolism:
The metabolism of fluoxetine, like that of a number of other compounds, including tricyclic antidepressants and some selective serotonin reuptake inhibitors (SSRIs), involves the P4502D6 system. Concomitant therapy with fluoxetine and the aforementioned drugs may lead to clinically significant drug interactions (see 9 DRUG INTERACTIONS section).

Accumulation and Slow Elimination:
The relatively slow elimination of fluoxetine and its active metabolite, norfluoxetine, results in significant accumulation of these active moieties in chronic use. Therefore, it may take up to 1 to 2 months for the active drug substance(s) to disappear from the body. This persistence of active moieties is important to keep in mind when Teva-Fluoxetine is discontinued, or when drugs that are predicted to interact with Teva-Fluoxetine are to be administered soon after its discontinuation (see 7 WARNINGS AND PRECAUTIONS, General, Implications of the Long Elimination Half-Life of Fluoxetine; and 9 DRUG INTERACTIONS sections).

Kinetic Data:
After 30 days of dosing at 20 mg/day, mean plasma concentrations of fluoxetine 79.1 ± 33.4 ng/mL and of norfluoxetine 129 ± 42.0 ng/mL have been observed. Plasma concentrations of fluoxetine (elimination half-life of 1 to 3 days after acute administration and 4 to 6 days after chronic administration) were higher than those predicted by single-dose studies. Norfluoxetine appears to have linear pharmacokinetics. Its mean terminal half-lives after a single dose and multiple doses were 8.6 days and 9.3 days, respectively.

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 at the same dose.

Protein Binding:
Approximately 94% of fluoxetine is protein bound. The interaction between fluoxetine and other highly protein bound drugs has not been fully evaluated, but may be important (see 9 DRUG INTERACTIONS section).

Special Populations and Conditions

Geriatrics : The effects of age upon the metabolism of fluoxetine have been investigated in a subset of 260 elderly, but otherwise healthy, depressed patients (mean age: 67.4 yr, range 60 to 85 yr) who received 20 mg fluoxetine for 6 weeks. Mean plasma concentrations were found to be 89.5 ± 53.6 ng/mL for fluoxetine and 119 ± 51.3 ng/mL for norfluoxetine. However, the effects of concomitant illness and/or concomitant drugs have not been evaluated.

- **Hepatic Insufficiency:** In patients with cirrhosis, the elimination half-life of fluoxetine was prolonged, with a mean of 7.6 days compared to a range of 2 to 3 days seen in healthy subjects; norfluoxetine half-life was also prolonged, with a mean of 12 days compared to a range of 7 to 9 days in healthy subjects. Fluoxetine should therefore be used with caution in patients with liver disease (see 4.2 Recommended Dose and Dosage Adjustment, Special Patient Populations; and 7 WARNINGS AND PRECAUTIONS, Hepatic sections).

- **Renal Insufficiency:** 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. However, with chronic administration, additional accumulation of fluoxetine or its metabolites (possibly including some not yet identified) may occur in patients with severely impaired renal function, and the use of a lower or less frequent dose is advised (see 4.2 Recommended Dose and Dosage Adjustment, Special Patient Populations; and 7 WARNINGS AND PRECAUTIONS, Renal sections).

11 STORAGE, STABILITY AND DISPOSAL

Bottles should be stored between 15-30°C. Preserve in tight and light-resistant containers. Keep out of reach and sight of children.

12 SPECIAL HANDLING INSTRUCTIONS

Not applicable.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

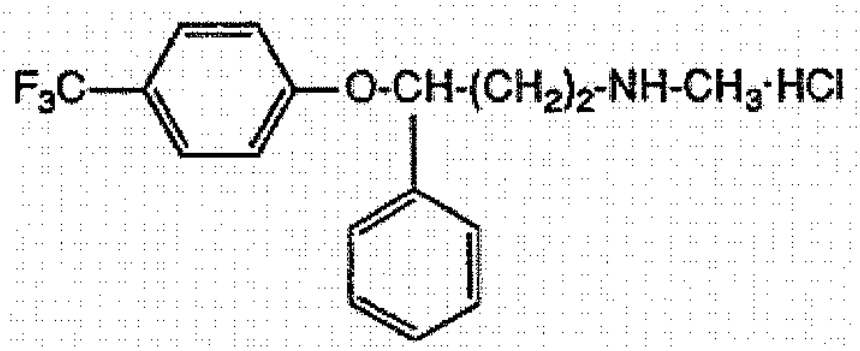
Drug Substance

Proper name: Fluoxetine hydrochloride

Chemical name: (+)-N-methyl-3-phenyl-3-[(α,α,α-trifluoro-p-tolyl)-oxy]-propylamine hydrochloride

Molecular formula and molecular weight: $C_{17}H_{18}F_3NO \cdot HC1$
345.79 g/mol

Structural formula:



Physiochemical properties:

Description:	Fluoxetine hydrochloride is a white to off-white almost odourless powder.
pKa:	9.5 (66% Dimethylformamide)
Solubility Profile:	It is freely soluble in methanol and in ethanol; soluble in chloroform; sparingly soluble in isopropanol; slightly soluble in water; practically insoluble in toluene, benzene and ethyl acetate.
Melting Point:	ranging from l53-l59°C.
pH	pH=5.0-7.0 (0.5% solution)

14 CLINICAL TRIALS

14.1 Trial Design and Study Demographics

Depression

- The efficacy of fluoxetine hydrochloride was established in 5- and 6- week placebo-controlled clinical trials in depressed outpatients (≥18 yr of age), who meet the DSM-III-R criteria for major depressive disorder.

- Two, 6-week placebo-controlled clinical trials in depressed elderly patients, who met the DSM-III-R criteria for major depressive disorder (mean age 67.4 yr, range 60 to 85 yr) have shown fluoxetine hydrochloride, 20 mg/day, to be effective.

- A study was conducted involving depressed outpatients who had responded (modified HAMD-17 score of ≤ 7 during each of the last 3 weeks of open-label treatment and absence of major depression by DSM-III-R criteria) by the end of an initial 12-week open treatment phase on fluoxetine hydrochloride 20 mg/day. These patients (N = 298) were randomized to continuation on double-blind fluoxetine hydrochloride 20 mg/day or placebo. At 38 weeks (50 weeks total), a statistically significantly lower relapse rate (defined as symptoms sufficient to meet a diagnosis of major depression for 2 weeks or a modified HAMD-17 score of ≥ 14 for 3 weeks) was observed for patients taking fluoxetine hydrochloride compared to those on placebo.

14.2 Study Results

See Section 14.1. Trial Design and Study Demographics.

14.3 Comparative bioavailability

A comparative two-way, crossover, bioavailability study was performed on two 20 mg fluoxetine capsule products, PrTeva-Fluoxetine 20 mg capsules and PROZAC® 20 mg capsules, in 12 normal healthy male volunteers. The pharmacokinetic plasma data for fluoxetine and norfluoxetine are tabulated below.

Fluoxetine hydrochloride
(2 X 20 mg)
From measured data

Geometric Mean
Arithmetic Mean (CV %)

Parameter	Test*	Reference†	% of PROZAC®
AUCO-72 hr (ng•hr/ml)	745.6 753.9 (16)	696.5 702.8 (14)	107%
AUC_T (ng•hr/ml)	828.8 856.9 (27)	772.8 810.3 (35)	107%
AUC_I (ng•hr/ml)	992.3 1024 (25)	934.5 974.9 (34)	106%

C_{MAX} (ng/mL)	20.49 20.89 (18)	19.89 20.21 (16)	103%
T_{MAX}§ (h)	8.33 (2)	8.67 (2)	-
$T_{½}$§ (h)	36.3 (13)	37.5 (22)	-

* Teva-Fluoxetine Capsules, Teva Canada Limited

† PROZAC® Manufactured by Eli Lily Canada Inc. (purchased in Canada).

§ Expressed as the arithmetic mean (CV%) only.

Fluoxetine hydrochloride
(2 X 20 mg)
From measured data

Geometric Mean
Arithmetic Mean (CV %)

Parameter	Test*	Reference†	% of PROZAC®
AUCO-72 hr (ng▪hr/ml)	827.3 877.6 (35)	842.5 904.4 (38)	98.2%
AUC_T (ng▪hr/ml)	3944 4093 (29)	3789 4006 (34)	104%
AUC_I (ng▪hr/ml)	4628 4739 (25)	4628 4789 (28)	100%
C_{MAX} (ng/mL)	15.03 15.82 (32)	14.88 15.61 (33)	101%
T_{MAX}§ (h)	7.20 (25)	63.3 (31)	-
$T_{½}$§ (h)	152.0 (44)	162.0 (47)	-

* Teva-Fluoxetine Capsules, Teva Canada Limited

† PROZAC® Manufactured by Eli Lily Canada Inc. (purchased in Canada).

§ Expressed as the arithmetic mean (CV%) only.

16 NON-CLINICAL TOXICOLOGY

General Toxicology:

Subchronic/Chronic/Carcinogenicity and Related Toxicity Studies:

Subchronic Toxicity Studies

Mice were maintained for three months on diets equivalent to ca. 2, 7 or 31 mg/kg/day. Significant effects were essentially limited to high dose mice and included 15% mortality; persistent hyperactivity and decreased body weight gain; slight and reversible increases in

alkaline phosphatase and alanine transaminase; decreases in testes, heart, and spleen weights; hypospermatogenesis; reversible pulmonary phospholipidosis.

Pulmonary histiocytosis (phospholipidosis) was the major pathological finding in rats maintained on diets providing average doses of approximately 9, 25 or 74 mg/kg/day for three months. All animals at ca. 74 mg/kg/day died by week 8. Decreased food consumption, weight loss, and hyperirritability were observed at ca. 25 and 74 mg/kg/day.

Dogs survived oral doses up to 20 mg/kg/day for three months with significant anorexia as the major treatment-related effect. Significant accumulation of both fluoxetine and norfluoxetine occurred in the plasma and tissues. Mydriasis and tremors were observed during the first month.

Monkeys given 10 or 25 mg/kg/day p.o. for two weeks exhibited anorexia and weight loss. One monkey at 25 mg/kg/day exhibited clonic convulsions after six doses. Accumulation of fluoxetine and norfluoxetine was observed after multiple dosing and decreased erythrocyte and white blood cell counts were observed.

Chronic Toxicity Studies

Fluoxetine was given daily to rats (25/sex/dose) for one year at dietary levels of ca. 0.5, 2.3 and 10.7 mg/kg/day. Physical signs of toxicity were limited to females at the high dose level and consisted of anorexia, chromodacryorrhea and an unusual behaviour first noted during the eighth month of treatment in which the animals walked on their toes with feet extended and backs arched after they had been handled.

Evidence of phospholipidosis was obtained in the lung, liver and adrenal cortex of 24/40 animals at the high dose level and in one rat at the mid-dose level. Phospholipidosis was reversible after two months' withdrawal from treatment. Minimal to slight fat deposition in the liver was prevalent at the mid and high dose levels. Reversible, minimal reticuloendothelial cell hyperplasia was present in the lymph nodes of the high dose level animals.

Dogs (5/sex/dose) received daily oral doses of 1, 4.5, or 20 mg/kg (decreased to 10 mg/kg after 6 months as three females died) of fluoxetine for one year. The toxic effects observed in this study were similar to those of the subchronic study except that phospholipidosis was seen after chronic administration in the lung, liver, adrenals, the inner plexiform layer of the retina, lymph nodes, spleen, and peripheral leukocytes in the animals receiving the high dose. They also showed moderate bradycardia and a moderate decrease in adrenal weight.

Phospholipidosis was only observed in the lung and leukocytes in a few of the dogs at the lowest dose level of 1.0 mg/kg/day. No cardiovascular effects were seen apart from a slight decrease in basal heart rate. All treatment-related effects were reversible during the recovery period in surviving animals.

Discussion on Phospholipidosis: Systemic phospholipidosis was associated with the subchronic and/or chronic administration of fluoxetine to mice, rats and dogs. This effect was associated with the accumulation of norfluoxetine, and to a lesser extent, fluoxetine, in affected tissues. Systemic phospholipidosis was not associated with any adverse effects and was shown to be reversible after the chronic administration of fluoxetine for one year in rats and dogs.

This effect has been demonstrated in animals with a number of other clinically useful cationic amphiphilic drugs including antidepressants - imipramine, clomipramine, iprindole and other drugs - chlorphentermine, fenfluramine, clozapine, chloroquine, mepacocine, chlorcyclizine, tamoxifen, 4,4'diethylaminoethoxyhexestrol, amiodarone and perhexiline. The significance of this finding for man is not fully understood. It is anticipated that in the clinical use of fluoxetine, the properties of the drug which are associated with phospholipidosis will not result in any untoward effect.

Carcinogenicity:
Rats were maintained for two years at dietary levels equivalent to a time-weighted average dose of ca. 0.45, 2 and 9 mg/kg/day. Age-related observations such as chromodacryorrhea, alopecia, and poor grooming increased at the high dose, especially in females. Weight gain and food consumption were depressed at the high dose and a handling-induced behaviour involving arching of the back and walking on toes was observed primarily in females in this group. Increased tissue levels of fluoxetine and norfluoxetine were observed at all doses, and phospholipidosis was observed primarily at the high dose. There were no significant increases in tumor incidence or animal mortality.

Mice were fed dietary levels of fluoxetine equivalent to ca. 1.2, 4.8 and 12.1 mg/kg/day. The dietary levels were based on the results of the three-month subchronic study. Unexpectedly, high mortality occurred in females receiving the high dose early in the two-year study, necessitating lowering the dose after 30 days. The survival rate of females receiving the high dose was reduced at two years. No major toxicological effects were seen in mice other than a moderate increase in alanine transaminase in males receiving the high dose and slight changes in organ weights. Hepatocellular degeneration, fat deposition in liver, and centrilobular hepatocellular degeneration were observed microscopically at the median and high dose. There was no evidence of phospholipid accumulation in the lung, and no oncogenic response was observed.

A second two-year mouse study using similar doses gave similar results. Survival at two years was reduced in females receiving the high dose. Handling-induced clonic convulsions occurred at all levels in males, and in females, at the high-dose level it was accompanied by a slight increase in liver weight. Minimal-to-moderate fatty change in the liver and hepatocellular cytomegaly were seen in mice from the median- and high-dose levels. There was a dose-dependent increase in concentrations of fluoxetine and norfluoxetine in lung tissue. There was no evidence of phospholipid accumulation in the lung, and no oncogenic response was observed.

Genotoxicity:
The mutagenicity of fluoxetine and its metabolite norfluoxetine was evaluated in a battery of *in vitro* and *in vivo* tests including Ames test, modified Ames test, DNA repair in rat hepatocytes, sister chromatid exchange in Chinese hamster bone marrow assays, and mouse lymphoma assay.
Fluoxetine and norfluoxetine were negative in all 5 systems.

Reproductive and Developmental Toxicology:

Reproductive and Impairment of Fertility Studies
Female Wistar rats (30/dose) were given daily oral doses of 2, 5, or 12.5 mg/kg from two weeks prior to mating through gestation or lactation. In a second study, male Wistar rats (40/dose) were maintained on diets approximately equivalent to 1.5, 3.9, or 9.7 mg/kg for 10 weeks prior to mating and through the breeding trial. These treated males were mated with female Wistar rats (40/dose) maintained at the same dietary levels for three weeks prior to mating and throughout lactation. In both studies, a depression in neonatal survival was obtained at the high dose level. No teratogenic effects or adverse effects on fertility or post-natal development were associated with fluoxetine administration.

Impairment of fertility in adult animals at doses up to 12.5 mg/kg/day (approximately 1.5 times the MRHD on a mg/m^2 basis) was not observed.

In a juvenile toxicology study, fluoxetine hydrochloride was administered orally to CD rats (30/sex/group) at doses of 0, 3, 10, and 30 mg/kg/day from postnatal days 21 through 91 and evaluated for general clinical observations. Ten rats/sex/group were necropsied on postnatal day 91 and evaluated for changes in clinical chemistry, hematology, femur length, organ weights, and histopathology. Following an approximately 11-week recovery period, sperm assessments were performed in all groups, and microscopic examination of testis and epididymides occurred in the 30 mg/kg/day males only.

Plasma levels achieved at 30 mg/kg/day were approximately 5 to 8 fold (fluoxetine) and 18 to 20 fold (norfluoxetine), and at 10 mg/kg approximately 2 fold (fluoxetine) and 8 fold (norfluoxetine) higher compared to plasma concentrations usually achieved in pediatric patients.

Administration of 30 mg/kg/day of fluoxetine hydrochloride on postnatal days 21 through 90 resulted in a substantial decrease in body weight gain with concomitant degeneration and necrosis of seminiferous tubules of the testis, epididymal epithelial vacuolation, epididymal sperm granuloma, and immaturity and inactivity of the female reproductive tract.

Findings following an approximately 11-week recovery period in male rats administered 30 mg/kg/day, consisted of testicular degeneration, seminiferous tubular sperm microgranulomas, epididymal epithelial cribriform change, epididymal epithelial vacuolation and epididymal sperm granulomas. All of the rats with cribriform change had testicular

degeneration, and comparison to the treatment-phase rats indicted that the testicular degeneration was irreversible. In contrast, the reduction in degree and extent of epididymal vacuolation compared to the treatment-phase rats indicates that the vacuolation was reversible.

Sperm assessments in the 30-mg/kg males only indicated an approximately 30% decrease in sperm concentrations without affecting sperm morphology or motility. Decreased fertility was observed in this dose-group. Delays in sexual maturation occurred in the 10-mg/kg/day males and in the 30-mg/kg/day males and females. The significance of these findings in humans is unknown.

Teratology Studies

Virgin female Fischer 344 rats (25/dose) were bred with untreated control males and were given daily oral (gavage) doses of 2, 5, or 12.5 mg/kg/day fluoxetine on gestation days 6-15; animals were evaluated on gestation day 20. Body weight gains and food consumption were depressed at 12.5 mg/kg/day. Fluoxetine produced no teratogenic effects and no changes in reproductive parameters.

Virgin female Dutch Belted rabbits (15/dose) were artificially inseminated with semen from untreated control males and were given daily oral (gavage) doses of 2.5, 7.5, or 15 mg/kg/day fluoxetine on gestation days 6-18; animals were evaluated on gestation day 28. Maternal toxicity was demonstrated by depressed body weight gains and food consumption at all dose levels in a dose-dependent manner. At the 15 mg/kg/day dose, two rabbits died and three aborted.

Resorptions were also increased in this group. There was no evidence of a teratogenic effect.

Juvenile Toxicity:

In a juvenile toxicology study in CD rats, administration of 30 mg/kg of fluoxetine hydrochloride on postnatal days 21 through 90 resulted in increased serum activities of creatine kinase (CK) and aspartate aminotransferase (AST), which were accompanied microscopically by skeletal muscle degeneration, necrosis and regeneration. Femur lengths at 30 mg/kg increased to a lesser extent compared with control rats. The dose of 30 mg/kg was associated with severe toxicity in general and exceeded a maximum tolerated dose. Other findings are discussed in the Reproductive and Impairment of Fertility Studies.

A specific effect of fluoxetine on bone development has been reported in mice treated with fluoxetine during the juvenile period. When mice were treated with fluoxetine (5 or 20 mg/kg, ip) for 4 weeks starting at 4 weeks of age, bone formation was reduced resulting in decreased bone mineral content and density. These doses did not affect overall growth (body weight gain or femoral length). The doses administered to juvenile mice in this study are approximately 0.5 and 2 times the MRD for pediatric patients on a body surface basis.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

[Pr]Teva-Fluoxetine
Fluoxetine Capsules, USP

Read this carefully before you start taking Teva-Fluoxetine and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about Teva-Fluoxetine.

What is Teva-Fluoxetine used for?
Teva-Fluoxetine is used to relieve your symptoms of:

- **Depression** (feeling sad, a change in appetite or weight, difficulty concentrating or sleeping, feeling tired, headaches, unexplained aches and pain)
- **Bulimia** (an eating disorder where you force yourself to vomit after eating
- **Obsessive-compulsive disorder** (recurrent and intrusive thought, feeling, ideas, or sensation; recurrent pattern of behaviour, or unwanted thoughts or actions)

How does Teva-Fluoxetine work?
Teva-Fluoxetine (fluoxetine) belongs to a group of medicines called selective serotonin reuptake inhibitors (SSRIs). Fluoxetine is thought to work by increasing the levels of a chemical in the brain called serotonin. This helps to relieve your symptoms of depression, bulimia and/or obsessive-compulsive disorder.

What are the ingredients in Teva-Fluoxetine?
Medicinal ingredients: fluoxetine hydrochloride.

Non-medicinal ingredients: Teva-Fluoxetine 10 mg capsules contain: colloidal silicon dioxide, magnesium stearate, pregelatinized starch and sodium starch glycolate.
The capsule shell contains: D & C yellow # 10, FD& C blue #1, FD & C yellow #6, gelatin, iron oxide black and titanium dioxide.

Teva-Fluoxetine 20 mg capsules contain: colloidal silicon dioxide, magnesium stearate, pregelatinized starch and sodium starch glycolate.
The capsule shell contains: D & C yellow # 10, FD& C blue #1, FD & C yellow #6, gelatin and titanium dioxide.

Teva-Fluoxetine comes in the following dosage forms:
Capsules; 10 mg and 20 mg

Do not use Teva-Fluoxetine if :

- you are allergic to fluoxetine hydrochloride or to any of the non-medicinal ingredients in Teva-Fluoxetine (see What are the ingredients in Teva-Fluoxetine:).
- You are currently or have recently taken the drug thioridazine.
- you are currently or have recently taken any monamine oxidase anti-depressants such as phenelzine sulphate, moclobemide, linezolid. If you are unsure, ask your healthcare professional.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take Teva-Fluoxetine. Talk about any health conditions or problems you may have, including if you:

- have anorexia
- have bipolar disorder

- have ever had an allergic reaction to any medication
- have QT/QTc prolongation or a family history of QT/QTc prolongation
- have a heart disease
- have a personal history of fainting spells
- have a family history of sudden cardiac death at less than 50 years of age
- have electrolyte disturbances (e.g., low blood potassium or magnesium levels) or conditions that could lead to electrolyte disturbances (e.g., vomiting, diarrhea, dehydration)
- have or have a history of a bleeding disorder or have been told that you have low platelets
- have or have a history of liver or kidney problems
- have or have a history of seizures
- have diabetes
- had a recent bone fracture or were told you have osteoporosis or risk factors for osteoporosis
- are pregnant, thinking about becoming pregnant, or if you are breast feeding
- drink alcohol and /or use street drugs

Other warnings you should know about:

During treatment with Teva-Fluoxetine, it is important that you and your doctor talk regularly about how you are feeling.

Do NOT stop taking Teva-Fluoxetine without talking to your healthcare professional first, as it may cause unwanted side effects such as headache, insomnia, numbness, tingling, burning, or prickling, nervousness, anxiety, nausea, sweating, dizziness, jitteriness and weakness.

New or worsened emotional or behavioural problems: When you first start taking Teva-Fluoxetine or when your dose is adjusted, you may feel worse instead of better. You may feel new or worsened feelings of agitation, hostility, anxiety, or impulsivity, Do NOT stop taking your medicine, it takes time for Teva-Fluoxetine to work.

Self-harm: If you have thoughts of harming or killing yourself at any time, contact your doctor or go to a hospital **right away**. You may find it helpful to tell a relative or close friend that you are depressed or have other mental illnesses. Ask them to read this leaflet. You might ask them to tell you if they:

- think your depression or mental illness is getting worse, or
- are worried about changes in your behaviour

Pregnancy: Only take Teva-Fluoxetine during pregnancy if you and your doctor have discussed the risks and have decided that you should. If you take Teva-Fluoxetine near the end of your pregnancy, you may be at a higher risk of heavy vaginal bleeding shortly after birth. If you become pregnant while taking Teva-Fluoxetine, tell your doctor **right away.**

Effects on newborns: In some cases, babies born to a mother taking Teva-Fluoxetine during pregnancy may require hospitalization, breathing support and tube feeding. Be ready to seek medical help for your newborn if they:

- Have trouble breathing or feeding,
- Have muscle stiffness, or floppy muscles (like a rag doll)
- Have seizures (fits)
- Are shaking (jitteriness)
- Are constantly crying

If you take Teva-Fluoxetine:

- During early pregnancy, there is a possible slight increased risk that your newborn may have a heart defect.
- During late pregnancy, your newborn may be at risk of having a serious lung condition called Persistent Pulmonary Hypertension of the Newborn (PPHN), which causes breathing problems.

Falls: Teva-Fluoxetine can cause you to feel sleepy or dizzy and can affect your balance. This increases your risk of falling, which can cause fractures or other fall related-injuries, especially if you:

- Take sedatives
- Consume alcohol
- Are elderly
- Have a condition that causes weakness or frailty

Driving and using machines: Teva-Fluoxetine may make you feel sleepy. Give yourself time after taking Teva-Fluoxetine to see how you feel before driving a vehicle or using machinery.

Teva-Fluoxetine can cause serious side effects including:

- Angle-closure glaucoma (sudden eye pain)
- Heart rhythm problems

See the **Serious side effects and what to do about them** table below for more information on these and other serious side effects.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with Teva-Fluoxetine:

Serious Drug Interactions
Do not use Teva-Fluoxetine if you are taking or have recently taken: • Monoamine oxidase inhibitor (e.g., phenelzine, tranylcypromine, moclobemide or selegiline, linezolid, methylene blue) • Thioridazine.

- drugs that affect how your heart beats such as quinidine, procainamide, disopyramide, amiodarone, sotalol, ibutilide, dronedarone, flecainide, propafenone
- drugs used to manage psychosis (antipsychotics) such as chlorpromazine, pimozide, haloperidol, droperidol, ziprasidone, clozapine
- drugs used to treat depression such as citalopram, venlafaxine, amitriptyline, imipramine, maprotiline, desipramine
- opioids and pain killers such as methadone, tramadol, fentanyl, tapentadol, meperidine, pentazocine
- drugs to treat bacterial infections such as erythromycin, clarithromycin, telithromycin, tacrolimus, moxifloxacin, levofloxacin, ciprofloxacin
- drugs used to treat fungal infections such as ketoconazole, fluconazole, voriconazole
- drugs used to treat malaria such as quinine, chloroquine
- drugs used to treat nausea and vomiting such as domperidone, dolasetron, ondansetron
- drugs used in cancer therapy such as vandetanib, sunitinib, nilotinib, lapatinib, vorinostat, tamoxifen
- drugs used to treat asthma such as salmeterol, formoterol

- drugs that affect your electrolyte levels such as diuretics ("water pills"), laxatives and enemas, amphotericin B, high dose corticosteroids (drugs that reduce inflammation)
- drugs that can affect how your blood clots such as warfarin, acetylsalicylic acid (Aspirin), non-steroidal anti-inflammatory drugs (NSAIDs)
- lithium, a drug used to treat bipolar disorder
- benzodiazepines such as diazepam, alprazolam
- drugs used to treat seizures such as carbamazepine, phenytoin
- drugs used to treat cough such as dextromethorphan
- tryptophan, a drug used to treat anxiety or used as a sleep aid
- sumatriptan, a drug used to treat migraines
- herbal medicines such as St. John's Wort
- alcohol

How to take Teva-Fluoxetine:

- It is very important that you take Teva-Fluoxetine exactly as your doctor has instructed.
- Teva-Fluoxetine may be taken with or without food.
- Swallow the capsules whole; do not chew or open them.
- Continue to take your medicine even if you do not feel better, as it may take a number of weeks for your medicine to start working.
- Keep taking your Teva-Fluoxetine until the doctor tells you to stop.

Remember, this medicine has been prescribed only for you. Do not give it to anybody else, as they may experience undesirable effects, which may be serious.

Usual dose:

Depression
Usual initial dose: 20 mg a day in the morning. Maximum dose: 60 mg a day.

Bulimia
60 mg a day.

Obsessive-Compulsive Disorder
20 to 60 mg a day.

Overdose:

If you think you, or a person you are caring for, have taken too much Teva-Fluoxetine, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

If you forget to take a dose of Teva-Fluoxetine, take it as soon as you remember. If it is almost time to take your next dose, skip the missed dose and take your next dose at the scheduled time. Do not try to make up for a missed dose by taking a double dose the next time.

What are possible side effects from using Teva-Fluoxetine?
These are not all the possible side effects you may have when taking Teva-Fluoxetine. If you experience any side effects not listed here, tell your healthcare professional.

- nausea
- dizziness

- headache
- anxiety
- nervousness
- drowsiness
- insomnia (difficulty falling or staying asleep)
- fatigue
- weakness
- tremors (shaking)
- light-headedness
- diarrhea
- upset stomach
- indigestion
- dry mouth
- loss of appetite
- excessive sweating
- rash or itchy skin
- low sex drive
- weight gain or loss

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
COMMON			
Allergic Reaction: difficulty swallowing or breathing, wheezing, feeling sick to your stomach and throwing up, hives or rash, swelling of the face, lips, tongue or throat.			✓
Allergic reactions (skin rash, hives alone)		✓	
Anorexia (an eating disorder): extremely low body weight, not eating, obsession with food, calories and dieting, excessive exercise		✓	
UNCOMMON			
Akathisia (a type of movement disorder): feeling restless, unable to sit or stand still		✓	
Hallucinations (seeing or hearing things that are not there)		✓	
Mania: elevated or irritable mood, decreased need for sleep, racing thoughts		✓	
Seizures (fits)**:** uncontrollable shaking with or without loss of consciousness			✓
Urinary retention (inability to pass urine or to empty the bladder): pain		✓	
RARE			
Angle-closure glaucoma (sudden eye pain): increased pressure in your eyes, eye and head pain, swelling or redness in or around the eye, hazy or blurred vision, sudden loss of sight			✓
Gastrointestinal Bleeding (bleeding in the stomach or bowels): black, tarry stool, blood in the stool			✓
Heart rhythm problems: dizziness, palpitations (rapid, pounding, or irregular heartbeat), fainting or seizures			✓

Serious side effects and what to do about them			
Hyponatremia (low sodium in the blood): lethargy, confusion, muscular twitching, achy, stiff or uncoordinated muscles, seizure, coma		✓	
Liver Disorder: yellowing of the skin or eyes, dark urine and pale stools, abdominal pain, nausea, vomiting, loss of appetite		✓	
Uncontrollable movements of the body or face		✓	
VERY RARE			
Serotonin Syndrome: agitation, hallucinations, confusion, or other changes in mental status; coordination problems, uncontrolled muscle spasms, or muscle twitching (overactive reflexes); restlessness, shivering, racing or fast heartbeat, high or low blood pressure, sweating or fever, nausea, vomiting, or diarrhea, stiff muscles, tremor, loss of muscle control			✓
UNKNOWN			
Increase in the hormone prolactin: In women: breast discomfort, leakage of milk from the breasts, missed periods, or other problems with your menstrual cycle. In men: decreased body and facial hair, breast swelling, difficulty in getting or maintaining erections, or other sexual dysfunction		✓	
New or worsened emotional or behavioural problems		✓	
Thrombocytopenia (low blood platelets): bruising or bleeding for longer than usual if you hurt yourself, fatigue and weakness		✓	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html)for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:
Keep all medicines out of the reach and sight of children. Teva-Fluoxetine in bottles should be stored between 15-30°C. Preserve in tight and light-resistant containers.

The expiry date of this medicine is printed on the package label. Do not use the medicine after the expiry date. If your doctor tells you to stop taking Teva-Fluoxetine or you find that they have passed their expiry date, please return any left over medicine to your pharmacist.

If you want more information about Teva-Fluoxetine:

- Talk to your healthcare professional.
- Find the full Product Monograph that is prepared for healthcare professionals and includes this Patient Medication by visiting the Health Canada website (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); the manufacturer's website http://www.tevacanada.com, or by calling 1-800-268-4127 ext 3; or email druginfo@tevacanada.com.

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