9.125" 17.0" W .625" .625" 6.625"

Width: 17.0"
Length: 18.75"
Fold: 1.25" x 1.25"

422-02-2024 FLUOXETINE TABLETS 60 MG

1.25"H x 1.25"W

18.75"L

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use FLUOXETINE TABLETS, safely and effectively. See full prescribing information for FLUOXETINE TABLETS.
FLUOXETINE tablets, for oral use
Initial U.S. Approval: 1987

WARNING: SUICIDAL THOUGHTS AND BEHAVIORS
See full prescribing information for complete boxed warning.
- **Increased risk of suicidal thinking and behavior in children, adolescents, and young adults taking antidepressants (5.1).**
- **Monitor for worsening and emergence of suicidal thoughts and behaviors (5.1).**

----------RECENT MAJOR CHANGES----------
Warnings and Precautions (5.2, 5.7) 8/2023

----------INDICATIONS AND USAGE----------
Fluoxetine tablets are a selective serotonin reuptake inhibitor (SSRI) indicated for the treatment of:
- Major Depressive Disorder (MDD) (1)
  - Adults: Efficacy was established in one 5-week trial, three 6-week trials, and one maintenance study (14.1)
  - Pediatrics: Efficacy was established in two 8- to 9-week trials of patients 8 to 18 years of age (14.1)
- Obsessive Compulsive Disorder (OCD) (1)
  - Adults: Efficacy was established in two 13-week trials (14.2)
  - Pediatrics: Efficacy was established in one 13-week trial in patients 7 to 17 years of age (14.2)
- Bulimia Nervosa (1)
  - Adults: Efficacy was established in two 8-week trials and one 16-week trial (14.3)
- Panic Disorder, with or without agoraphobia (1)
  - Adults: Efficacy was established in two 12-week trials (14.4)

----------DOSAGE AND ADMINISTRATION----------
- Use another fluoxetine product for initial doses of 10 mg/day to 20 mg/day or for doses other than 30 mg or 60 mg:

Indication	Adult	Pediatric
MDD (2.1)	20 mg/day in morning (initial dose) 20 mg/day (target dose) 80 mg/day (maximum dose studied)	10 mg/ day to 20 mg/day (initial dose)* *This product has not been studied in doses greater than 20 mg/day in pediatric MDD.
OCD (2.2)	20 mg/day in morning (initial dose) 20 to 60 mg/day (target dose)	10 mg/day (initial dose) 10 mg/day to 60 mg/day (target dose)
Bulimia Nervosa (2.3)	60 mg/day in morning	--
Panic Disorder (2.4)	10 mg/day (initial dose) 20 mg/day (target dose) 60 mg/day (maximum dose studied)	--

- No additional benefits seen at higher doses above 20 mg/day in MDD (2.1, 14.1)
- Use a lower or less frequent dosage in patients with hepatic impairment, the elderly, and for patients with concurrent disease or on multiple concomitant medications (2.5, 8.6)

----------DOSAGE FORMS AND STRENGTHS----------
- *Tablets:* 60 mg, functionally scored (3)

----------CONTRAINDICATIONS----------
- Monoamine Oxidase Inhibitors (MAOIs): Do not use MAOIs intended to treat psychiatric disorders with fluoxetine or within 5 weeks of stopping treatment with fluoxetine. Do not use fluoxetine within 14 days of stopping an MAOI intended to treat psychiatric disorders. In addition, do not start fluoxetine in a patient who is being treated with linezolid orintravenous methylene blue (4.1, 7.1)
- *Pimozide* (4.2, 5.11, 7.6, 7.7)
- *Thioridazine:* Do not use concomitantly with or within 5 weeks of discontinuing fluoxetine (4.2, 5.11, 7.6, 7.7)
- Known hypersensitivity to fluoxetine products (4.2, 5.3)

----------WARNINGS AND PRECAUTIONS----------
- *Suicidal Thoughts and Behaviors in Children, Adolescents, and Young Adults:* Monitor for clinical worsening and suicidal thinking and behavior (5.1)
- *Serotonin Syndrome:* Serotonin syndrome has been reported with SSRIs and serotonin-norepinephrine reuptake inhibitors (SNRIs), including fluoxetine, both when taken alone, but especially when co-administered with other serotonergic agents. If such symptoms occur, discontinue fluoxetine and serotonergic agents and initiate supportive treatment. If concomitant use of fluoxetine with other serotonergic drugs is clinically warranted, patients should be made aware of a potential increased risk for serotonin syndrome, particularly during treatment initiation and dose increases (5.2)
- *Activation of Mania/Hypomania:* Screen for Bipolar Disorder and monitor for mania/hypomania (5.4)
- *Seizures:* Use cautiously in patients with a history of seizures or with conditions that potentially lower the seizure threshold (5.5)
- *Altered Appetite and Weight:* Significant weight loss has occurred (5.6)
- *Increased Risk of Bleeding:* May increase the risk of bleeding. Use with NSAIDs, aspirin, warfarin, or drugs that affect coagulation may potentiate the risk of gastrointestinal or other bleeding (5.7, 7.4)
- *Angle-closure Glaucoma:* Angle-closure glaucoma has occurred in patients with untreated anatomically narrow angles treated with antidepressants (5.8)
- *Hyponatremia:* Has been reported with fluoxetine in association with syndrome of inappropriate antidiuretic hormone (SIADH). Consider discontinuing if symptomatic hyponatremia occurs (5.9)
- *QT Prolongation:* QT prolongation and ventricular arrhythmia including Torsades de Pointes have been reported with fluoxetine use. Use with caution in conditions that predispose to arrhythmias or increase fluoxetine exposure. Use cautiously in patients with risk factors for QT prolongation (4.2, 5.11, 7.6, 7.7, 10)
- *Long Half-life:* Changes in dose will not be fully reflected in plasma for several weeks (5.14)
- *Sexual Dysfunction:* Fluoxetine may cause symptoms of sexual dysfunction (5.16)

----------ADVERSE REACTIONS----------
Most common adverse reactions (≥ 5% and at least twice that for placebo): abnormal dreams, abnormal ejaculation, anorexia, anxiety, asthenia, diarrhea, dry mouth, dyspepsia, flu syndrome, impotence, insomnia, libido decreased, nausea, nervousness, pharyngitis, rash, sinusitis, somnolence, sweating, tremor, vasodilatation, and yawn (6.1)
To report SUSPECTED ADVERSE REACTIONS, contact ScieGen Pharmaceuticals Inc at 1-855-724-3436 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

----------DRUG INTERACTIONS----------
- *Drugs Metabolized by CYP2D6:* Fluoxetine is a potent inhibitor of CYP2D6 enzyme pathway (7.6)
- *Tricyclic Antidepressants (TCAs):* Monitor TCA levels during co-administration with fluoxetine or when fluoxetine has been recently discontinued (5.2, 7.6)
- *Benzodiazepines:* Diazepam – increased t., alprazolam - further psychomotor performance decrement due to increased levels (7.6)
- *Antipsycotics:* Potential for elevation of haloperidol and clozapine levels (7.6)
- *Anticonvulsants:* Potential for elevated phenytoin and carbamazepine levels and clinical anticonvulsant toxicity (7.6)
- *Serotonergic Drugs:* (2.6, 2.7, 4.1, 5.2)
- *Drugs that Prolong the QT Interval:* Do not use fluoxetine with thioridazine or pimozide. Use with caution in combination with other drugs that prolong the QT interval (4.2, 5.11, 7.6, 7.7)

----------USE IN SPECIFIC POPULATIONS----------
- *Pregnancy:* SSRI use, particularly later in pregnancy, may increase risk for persistent pulmonary hypertension and symptoms of poor adaptation (respiratory distress, temperature instability, feeding difficulty, hypotonia, tremor, irritability) in the neonate (8.1)
- *Pediatric Use:* Safety and effectiveness of fluoxetine in patients < 8 years of age with MDD and < 7 years of age with OCD have not been established (8.4).

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide

Revised: 2/2024

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FULL PRESCRIBING INFORMATION

WARNING: SUICIDAL THOUGHTS AND BEHAVIORS
- **Antidepressants increased the risk of suicidal thoughts and behavior in children, adolescents, and young adults in short-term studies. These studies did not show an increase in the risk of suicidal thoughts and behavior with antidepressant use in patients over age 24; there was a reduction in risk with antidepressant use in patients aged 65 and older *[see Warnings and Precautions (5.1)]*.**
- **In patients of all ages who are started on antidepressant therapy, monitor closely for worsening and for emergence of suicidal thoughts and behavior. Advise families and caregivers of the need for close observation and communication with the prescriber *[see Warnings and Precautions (5.1)]*.**
- **Fluoxetine is not approved for use in children less than 7 years of age *[see Warnings and Precautions (5.1) and Use in Specific Populations (8.4)]*.**

1 INDICATIONS AND USAGE
Fluoxetine tablets are indicated for the treatment of:
- Major Depressive Disorder (MDD). The efficacy of fluoxetine in MDD was established in one 5-week trial, three 6-week trials, and one maintenance study in adults. The efficacy of fluoxetine was also established in two 8- to 9-week trials in pediatric patients 8 to 18 years of age *[see Clinical Studies (14.1)]*.
- Obsessions and compulsions in patients with Obsessive Compulsive Disorder (OCD). The efficacy of fluoxetine in OCD was demonstrated in two 13-week trials in adults and one 13-week trial in pediatric patients 7 to 17 years of age *[see Clinical Studies (14.2)]*.
- Binge-eating and vomiting behaviors in patients with moderate to severe Bulimia Nervosa. The efficacy of fluoxetine in Bulimia Nervosa was demonstrated in two 8-week trials and one 16-week trial in adults *[see Clinical Studies (14.3)]*.
- Panic Disorder, with or without agoraphobia. The efficacy of fluoxetine in Panic Disorder was demonstrated in two 12-week trials in adults *[see Clinical Studies (14.4)]*.

2 DOSAGE AND ADMINISTRATION
This product is only available in a 60-mg dosage form. A 30-mg dose may be achieved with one-half of the scored tablet. Use of this product requires initial titration with another fluoxetine product according to the dosing guidelines indicated below.

2.1 Major Depressive Disorder
Initial Treatment
Adult - Initiate fluoxetine 20 mg/day orally in the morning. Consider a dose increase after several weeks if insufficient clinical improvement is observed. Administer doses above 20 mg/day once daily in the morning or twice daily (ie, morning and noon). The maximum fluoxetine dose should not exceed 80 mg/day.
In controlled trials used to support the efficacy of fluoxetine, patients were administered morning doses ranging from 20 mg/day to 80 mg/day. Studies comparing fluoxetine 20 mg/day, 40 mg/day, and 60 mg/day to placebo indicate that 20 mg/day is sufficient to obtain a satisfactory response in MDD in most cases *[see Clinical Studies (14.1)]*.
Pediatric (children and adolescents) - Treatment should be initiated with a dose of 10 mg/day or 20 mg/day. After 1 week at 10 mg/day, the dose should be increased to 20 mg/day. However, due to higher plasma levels in lower weight children, the starting and target dose in this group may be 10 mg/day. A dose increase to 20 mg/day may be considered after several weeks if insufficient clinical improvement is observed. In the short-term (8- to 9-week) controlled clinical trials of fluoxetine supporting its effectiveness in the treatment of MDD, patients were administered fluoxetine doses of 10 mg/day to 20 mg/day *[see Clinical Studies (14.1)]*. Doses greater than
20 mg/day have not been studied in pediatric patients with MDD. This product is only available in a 60-mg dosage form. Administration of doses with demonstrated efficacy of fluoxetine 10 mg/day to 20 mg/day in pediatric MDD requires the use of another formulation.
All Patients - As with other drugs effective in the treatment of MDD, the full effect may be delayed until 4 weeks of treatment or longer.
Periodically reassess to determine the need for maintenance treatment.
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 fluoxetine is co-administered or has been recently discontinued *[see Warnings and Precautions (5.2) and Drug Interactions (7.6)]*.

2.2 Obsessive Compulsive Disorder
Initial Treatment
Adults - Initiate fluoxetine 20 mg/day, orally in the morning. Consider a dose increase after several weeks if insufficient clinical improvement is observed. The full therapeutic effect may be delayed until 5 weeks of treatment or longer. Doses above 20 mg/day may be administered on a once daily (ie, morning) or twice daily schedule (ie, morning and noon). A dose range of 20 mg/day to 60 mg/day is recommended; however, doses of up to 80 mg/day have been well tolerated in open studies of OCD. The maximum fluoxetine dose should not exceed 80 mg/day.
In the controlled clinical trials of fluoxetine supporting its effectiveness in the treatment of OCD, patients were administered fixed daily doses of 20 mg, 40 mg, or 60 mg of fluoxetine or placebo *[see Clinical Studies (14.2)]*. In one of these studies, no dose-response relationship for effectiveness was demonstrated.
Pediatric (children and adolescents) - In adolescents and higher weight children, treatment should be initiated with a dose of 10 mg/day. After 2 weeks, the dose should be increased to 20 mg/day. Additional dose increases may be considered after several more weeks if insufficient clinical improvement is observed. A dose range of 20 mg/day to 60 mg/day is recommended.
In lower weight children, treatment should be initiated with a dose of 10 mg/day. Additional dose increases may be considered after several more weeks if insufficient clinical improvement is observed. A dose range of 20 mg/day to 30 mg/day is recommended. Experience with daily doses greater than 20 mg is very minimal, and there is no experience with doses greater than 60 mg.
In the controlled clinical trial of fluoxetine supporting its effectiveness in the treatment of OCD, patients were administered fluoxetine doses in the range of 10 mg/day to 60 mg/day *[see Clinical Studies (14.2)]*.
Periodically reassess to determine the need for treatment.

2.3 Bulimia Nervosa
Initial Treatment - Administer fluoxetine 60 mg/day in the morning. For some patients it may be advisable to titrate up to this target dose over several days. Fluoxetine doses above 60 mg/day have not been systematically studied in patients with Bulimia Nervosa. In the controlled clinical trials of fluoxetine supporting its effectiveness in the treatment of Bulimia Nervosa, patients were administered fixed daily fluoxetine doses of 20 mg or 60 mg, or placebo *[see Clinical Studies (14.3)]*. Only the 60-mg dose was statistically significantly superior to placebo in reducing the frequency of binge-eating and vomiting.
Periodically reassess to determine the need for maintenance treatment.

2.4 Panic Disorder
Initial Treatment- Treatment should be initiated with a dose of 10 mg/day. After 1 week, the dose should be increased to 20 mg/day. A dose increase may be considered after several weeks if no clinical improvement is observed. Fluoxetine doses above 60 mg/day have not been systematically evaluated in patients with Panic Disorder. In the controlled clinical trials of fluoxetine supporting its effectiveness in the treatment of Panic Disorder, patients were administered fluoxetine doses in the range of 10 mg/day to 60 mg/day *[see Clinical Studies (14.4)]*. The most frequently administered dose in the 2 flexible-dose clinical trials was 20 mg/day.
Periodically reassess to determine the need for continued treatment.

2.5 Dosing in Specific Populations
Geriatrics-A lower or less frequent dosage should be considered for the elderly *[see Use in Specific Populations (8.5)]*.
Hepatic Impairment-As with many other medications, a lower or less frequent dosage should be used in patients with hepatic impairment *[see Clinical Pharmacology (12.3) and Use in Specific Populations (8.6)]*.

2.6 Switching a Patient To or From a Monoamine Oxidase Inhibitor (MAOI) Intended to Treat Psychiatric Disorders
At least 14 days should elapse between discontinuation of an MAOI intended to treat psychiatric disorders and initiation of therapy with fluoxetine. Conversely, at least 5 weeks should be allowed after stopping fluoxetine before starting an MAOI intended to treat psychiatric disorders *[see Contraindications (4.1)]*.

2.7 Use of Fluoxetine with Other MAOIs Such as Linezolid or Methylene Blue
Do not start fluoxetine in a patient who is being treated with linezolid or intravenous methylene blue because there is an increased risk of serotonin syndrome. In a patient who requires more urgent treatment of a psychiatric condition, other interventions, including hospitalization, should be considered *[see Contraindications (4.1)]*.
In some cases, a patient already receiving fluoxetine therapy may require urgent treatment with linezolid or intravenous methylene blue. If acceptable alternatives to linezolid or intravenous methylene blue treatment are not available and the potential benefits of linezolid or intravenous methylene blue treatment are judged to outweigh the risks of serotonin syndrome in a particular patient, fluoxetine should be stopped promptly, and linezolid or intravenous methylene blue can be administered. The patient should be monitored for symptoms of serotonin syndrome for 5 weeks or until 24 hours after the last dose of linezolid or intravenous methylene blue, whichever comes first. Therapy with fluoxetine may be resumed 24 hours after the last dose of linezolid or intravenous methylene blue *[see Warnings and Precautions (5.2)]*.
The risk of administering methylene blue by nonintravenous routes (such as oral tablets or by local injection) or in intravenous doses much lower than 1 mg/kg with fluoxetine is unclear. The clinician should, nevertheless, be aware of the possibility of emergent symptoms of serotonin syndrome with such use *[see Warnings and Precautions (5.2)]*.

3 DOSAGE FORMS AND STRENGTHS
Tablets: 60 mg (fluoxetine base equivalent), film coated, functionally scored, capsule-shaped, white tablets debossed with "SG 422" on one side and plain on other side.

4 CONTRAINDICATIONS
4.1 Monoamine Oxidase Inhibitors (MAOIs)
The use of MAOIs intended to treat psychiatric disorders with fluoxetine or within 5 weeks of stopping treatment with fluoxetine is contraindicated because of an increased risk of serotonin syndrome. The use of fluoxetine within 14 days of stopping an MAOI intended to treat psychiatric disorders is also contraindicated *[see Dosage and Administration (2.6) and Warnings and Precautions (5.2)]*.
Starting fluoxetine in a patient who is being treated with MAOIs such as linezolid or intravenous methylene blue is also contraindicated because of an increased risk of serotonin syndrome *[see Dosage and Administration (2.7) and Warnings and Precautions (5.2)]*.

4.2 Other Contraindications
The use of fluoxetine is contraindicated with the following:
- Pimozide *[see Warnings and Precautions (5.11) and Drug Interactions (7.6, 7.7)]*
- Thioridazine *[see Warnings and Precautions (5.11) and Drug Interactions (7.6, 7.7)]*

Pimozide and thioridazine prolong the QT interval. Fluoxetine can increase the levels of pimozide and thioridazine through inhibition of CYP2D6. Fluoxetine can also prolong the QT interval.
- Known hypersensitivity to fluoxetine: Do not use this product in patients with known hypersensitivity to fluoxetine due to risk of anaphylactoid reactions, including bronchospasm, angioedema, laryngospasm, and urticaria *[see Warnings and Precautions (5.3)]*.

5 WARNINGS AND PRECAUTIONS
5.1 Suicidal Thoughts and Behaviors in Children, Adolescents, and Young Adults
Patients with MDD, both adult and pediatric, may experience worsening of their depression and/or the emergence of suicidal ideation and behavior (suicidality) or unusual changes in behavior, whether or not they are taking antidepressant medications, and this risk may persist until significant remission occurs. Suicide is a known risk of depression and certain other psychiatric disorders, and these disorders themselves are the strongest predictors of suicide. There has been a long-standing concern, however, that antidepressants may have a role in inducing worsening of depression and the emergence of suicidality in certain patients during the early phases of treatment. Pooled analyses of short-term placebo-controlled trials of antidepressant drugs (SSRIs and others) showed that these drugs increase the risk of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults (ages 18 to 24) with MDD and other psychiatric disorders. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction with antidepressants compared to placebo in adults aged 65 and older.
The pooled analyses of placebo-controlled trials in children and adolescents with MDD, OCD, or other psychiatric disorders included a total of 24 short-term trials of 9 antidepressant drugs in over 4,400 patients. The pooled analyses of placebo-controlled trials in adults with MDD or other psychiatric disorders included a total of 295 short-term trials (median duration of 2 months) of 11 antidepressant drugs in over 77,000 patients. There was considerable variation in risk of suicidality among drugs, but a tendency toward an increase in the younger patients for almost all drugs studied. There were differences in absolute risk of suicidality across the different indications, with the highest incidence in MDD. The risk differences (drug versus placebo), however, were relatively stable within age strata and across indications. These risk differences (drug-placebo difference in the number of cases of suicidality per 1000 patients treated) are provided in *Table 1*.

Table 1: Risk Differences in the Number of Suicidality Cases by Age Group in the Pooled Placebo-controlled Trials of Antidepressants in Pediatric and Adult Patients

Age Range (years)	Drug-Placebo Difference in Number of Cases of Suicidality per 1000 Patients Treated
	Increases Compared to Placebo
<18	14 additional cases
18-24	5 additional cases
	Decreases Compared to Placebo
25-64	1 fewer case
≥65	6 fewer cases

No suicides occurred in any of the pediatric trials. There were suicides in the adult trials, but the number was not sufficient to reach any conclusion about drug effect on suicide.
It is unknown whether the suicidality risk extends to longer-term use, i.e., beyond several months. However, there is substantial evidence from placebo-controlled maintenance trials in adults with depression that the use of antidepressants can delay the recurrence of depression.
All patients being treated with antidepressants for any indication should be monitored appropriately and observed closely for clinical worsening, suicidality, and unusual changes in behavior, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases.
The following symptoms, anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, and mania, have been reported in adult and pediatric patients being treated with antidepressants for MDD as well as for other indications, both psychiatric and nonpsychiatric. Although a causal link between the emergence of such symptoms and either the worsening of depression and/or the emergence of suicidal impulses has not been established, there is concern that such symptoms may represent precursors to emerging suicidality.
Consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medication, in patients whose depression is persistently worse, or who are experiencing emergent suicidality or symptoms that might be precursors to worsening depression or suicidality, especially if these symptoms are severe, abrupt in onset, or were not part of the patient's presenting symptoms.
If the decision has been made to discontinue treatment, medication should be tapered, as rapidly as is feasible, but with recognition that abrupt discontinuation can be associated with certain symptoms *[see Warnings and Precautions (5.15)]*.
Families and caregivers of patients being treated with antidepressants for MDD or other indications, both psychiatric and nonpsychiatric, should be alerted about the need to monitor patients for the emergence of agitation, irritability, unusual changes in behavior, and the other symptoms described above, as well as the emergence of suicidality, and to report such symptoms immediately to health care providers. Such monitoring should include daily observation by families and caregivers. Prescriptions for fluoxetine should be written for the smallest quantity of tablets consistent with good patient management, in order to reduce the risk of overdose.
It should be noted that fluoxetine is approved in the pediatric population only for MDD and OCD.

5.2 Serotonin Syndrome
Selective serotonin reuptake inhibitors (SSRIs), including fluoxetine, can precipitate serotonin syndrome, a potentially life-threatening condition. The risk is increased with concomitant use of other serotonergic drugs (including triptans, tricyclic antidepressants, fentanyl, lithium, tramadol, meperidine, methadone, tryptophan, buspirone, amphetamines, and St. John's Wort) and with drugs that impair metabolism of serotonin, i.e., MAOIs *[see Contraindications (4), Drug Interactions (7.1, 7.3)]*. Serotonin syndrome can also occur when these drugs are used alone.
Serotonin syndrome signs and symptoms may include mental status changes (e.g., agitation, hallucinations, delirium, and coma), autonomic instability (e.g., tachycardia, labile blood pressure, dizziness, diaphoresis, flushing, hyperthermia), neuromuscular symptoms (e.g., tremor, rigidity, myoclonus, hyperreflexia, incoordination), seizures, and gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea).
The concomitant use of fluoxetine with MAOIs is contraindicated. In addition, do not initiate fluoxetine in a patient being treated with MAOIs such as linezolid or intravenous methylene blue. No reports involved the administration of methylene blue by other routes (such as oral tablets or local tissue injection). If it is necessary to initiate treatment with an MAOI such as linezolid or intravenous methylene blue in a patient taking fluoxetine, discontinue fluoxetine before initiating treatment with the MAOI *[see Contraindications (4), Drug Interactions (7.1)]*.
Monitor all patients taking fluoxetine for the emergence of serotonin syndrome. Discontinue treatment with fluoxetine and any concomitant serotonergic agents immediately if the above symptoms occur, and initiate supportive symptomatic treatment. If concomitant use of fluoxetine with other serotonergic drugs is clinically warranted, inform patients of the increased risk for serotonin syndrome and monitor for symptoms.

5.3 Allergic Reactions and Rash
In US fluoxetine clinical trials, 7% of 10,782 patients developed various types of rashes and/or urticaria. Among the cases of rash and/or urticaria reported in premarketing clinical trials, 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 rash include 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 reactions were reported to recover completely.
In premarketing clinical trials, 2 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, a severe desquamating syndrome that was considered variously to be a vasculitis or erythema multiforme. Other patients have had systemic syndromes suggestive of serum sickness.
Since the introduction of fluoxetine, systemic reactions, possibly related to vasculitis and including lupus-like syndrome, have developed in patients with rash. Although these reactions are rare, they may be serious, involving the lung, kidney, or liver. Death has been reported to occur in association with these systemic reactions.
Anaphylactoid reactions, including bronchospasm, angioedema, laryngospasm, and urticaria alone and in combination, have been reported.
Pulmonary reactions, including inflammatory processes of varying histopathology and/or fibrosis, have been reported rarely. These reactions have occurred with dyspnea as the only preceding symptom.
Whether these systemic reactions 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 reactions has not been identified. Upon the appearance of rash or of other possibly allergic phenomena for which an alternative etiology cannot be identified, fluoxetine should be discontinued.

5.4 Screening Patients for Bipolar Disorder and Monitoring for Mania/Hypomania
A major depressive episode may be the initial presentation of Bipolar Disorder. It is generally believed (though not established in controlled trials) that treating such an episode with an antidepressant alone may increase the likelihood of precipitation of a mixed/manic episode in patients at risk for Bipolar Disorder. Whether any of the symptoms described for clinical worsening and suicide risk represent such a conversion is unknown. However, prior to initiating treatment with an antidepressant, patients with depressive symptoms should be adequately screened to determine if they are at risk for Bipolar Disorder; such screening should include a detailed psychiatric history, including a family history of suicide, Bipolar Disorder, and depression. Fluoxetine monotherapy is not indicated for the treatment of depressive episodes associated with Bipolar I Disorder.
In US placebo-controlled clinical trials for MDD, mania/hypomania was reported in 0.1% of patients treated with fluoxetine and 0.1% of patients treated with placebo. Activation of mania/hypomania has also been reported in a small proportion of patients with Major Affective Disorder treated with other marketed drugs effective in the treatment of MDD *[see Use in Specific Populations (8.4)]*.
In US placebo-controlled clinical trials for OCD, mania/hypomania was reported in 0.8% of patients treated with fluoxetine and no patients treated with placebo. No patients reported mania/hypomania in US placebo-controlled clinical trials for bulimia. In US fluoxetine clinical trials, 0.7% of 10,782 patients reported mania/hypomania *[see Use in Specific Populations (8.4)]*.

5.5 Seizures
In US placebo-controlled clinical trials for MDD, convulsions (or reactions described as possibly having been seizures) were reported in 0.1% of patients treated with fluoxetine and 0.2% of patients treated with placebo. No patients reported convulsions in US placebo-controlled clinical trials for either OCD or bulimia. In US fluoxetine clinical trials, 0.2% of 10,782 patients reported convulsions. The percentage appears to be similar to that associated with other marketed drugs effective in the treatment of MDD. Fluoxetine should be introduced with care in patients with a history of seizures. There have been rare reports of prolonged seizures in patients taking fluoxetine who are also receiving electroconvulsive therapy (ECT) treatment.

5.6 Altered Appetite and Weight
Significant weight loss, especially in underweight depressed or bulimic patients, may be an undesirable result of treatment with fluoxetine.
In US placebo-controlled clinical trials for MDD, 11% of patients treated with fluoxetine and 2% of patients treated with placebo reported anorexia (decreased appetite). Weight loss was reported in 1.4% of patients treated with fluoxetine and in 0.5% of patients treated with placebo. However, only rarely have patients discontinued treatment with fluoxetine because of anorexia or weight loss *[see Use in Specific Populations (8.4)]*.
In US placebo-controlled clinical trials for OCD, 17% of patients treated with fluoxetine and 10% of patients treated with placebo reported anorexia (decreased appetite). One patient discontinued treatment with fluoxetine because of anorexia *[see Use in Specific Populations (8.4)]*.
In US placebo-controlled clinical trials for Bulimia Nervosa, 8% of patients treated with fluoxetine 60 mg and 4% of patients treated with placebo reported anorexia (decreased appetite). Patients treated with fluoxetine 60 mg on average lost 0.45 kg compared with a gain of 0.16 kg by patients treated with placebo in the 16-week double-blind trial. Weight change should be monitored during therapy.

5.7 Increased Risk of Bleeding
SNRIs and SSRIs, including fluoxetine, may increase the risk of bleeding reactions. Concomitant use of aspirin, nonsteroidal anti-inflammatory drugs, warfarin, and other anti-coagulants may add to this 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. Based on data from the published observational studies, exposure to SSRIs, particularly in the month before delivery, has been associated with a less than 2-fold increase in the risk of postpartum hemorrhage *[see Use in Specific Populations (8.1)]*. Bleeding reactions related to SNRIs and SSRIs use have ranged from ecchymoses, hematomas, epistaxis, and petechiae to life-threatening hemorrhages.
Patients should be cautioned about the increased risk of bleeding associated with the concomitant use of fluoxetine and NSAIDs, aspirin, warfarin, or other drugs that affect coagulation *[see Drug Interactions (7.4)]*.

5.8 Angle-Closure Glaucoma
The pupillary dilation that occurs following use of many antidepressant drugs including fluoxetine may trigger an angle closure attack in a patient with anatomically narrow angles who does not have a patent iridectomy.

5.9 Hyponatremia
Hyponatremia has been reported during treatment with SNRIs and SSRIs, including fluoxetine. In many cases, this hyponatremia appears to be the result of the syndrome of inappropriate antidiuretic hormone secretion (SIADH). Cases with serum sodium lower than 110 mmol/L have been reported and appeared to be reversible when fluoxetine was discontinued. Elderly patients may be at greater risk of developing hyponatremia with SNRIs and SSRIs. Also, patients taking diuretics or who are otherwise volume-depleted may be at greater risk *[see Use in Specific Populations (8.5)]*. Discontinuation of fluoxetine should be considered in patients with symptomatic hyponatremia and appropriate medical intervention should be instituted.
Signs and symptoms of hyponatremia include headache, difficulty concentrating, memory impairment, confusion, weakness, and unsteadiness, which may lead to falls. More severe and/or acute cases have been associated with hallucination, syncope, seizure, coma, respiratory arrest, and death.

5.10 Anxiety and Insomnia
In US placebo-controlled clinical trials for MDD, 12% to 16% of patients treated with fluoxetine and 7% to 9% of patients treated with placebo reported anxiety, nervousness, or insomnia.
In US placebo-controlled clinical trials for OCD, insomnia was reported in 28% of patients treated with fluoxetine and in 22% of patients treated with placebo. Anxiety was reported in 14% of patients treated with fluoxetine and in 7% of patients treated with placebo.
In US placebo-controlled clinical trials for Bulimia Nervosa, insomnia was reported in 33% of patients treated with fluoxetine 60 mg, and 13% of patients treated with placebo. Anxiety and nervousness were reported, respectively, in 15% and 11% of patients treated with fluoxetine 60 mg and in 9% and 5% of patients treated with placebo.
Among the most common adverse reactions associated with discontinuation (incidence at least twice that for placebo and at least 1% for fluoxetine in clinical trials collecting only a primary reaction associated with discontinuation) in US placebo-controlled fluoxetine clinical trials were anxiety (2% in OCD), insomnia (1% in combined indications and 2% in bulimia), and nervousness (1% in MDD) *[Table 4]*.

5.11 QT Prolongation
Postmarketing cases of QT interval prolongation and ventricular arrhythmia including Torsades de Pointes have been reported in patients treated with fluoxetine. Fluoxetine should be used with caution in patients with congenital long QT syndrome; a previous history of QT prolongation; a family history of long QT syndrome or sudden cardiac death; and other conditions that predispose to QT prolongation and ventricular arrhythmia. Such conditions include concomitant use of drugs that prolong the QT interval; hypokalemia or hypomagnesemia; recent myocardial infarction, uncompensated heart failure, bradyarrhythmias, and other significant arrhythmias; and conditions that predispose to increased fluoxetine exposure (overdose, hepatic impairment, use of CYP2D6 inhibitors, CYP2D6 poor metabolizer status, or use of other highly protein-bound drugs). Fluoxetine is primarily metabolized by CYP2D6 *[see Contraindications (4.2), Drug Interactions (7.6, 7.7), Overdose (10.1), and Clinical Pharmacology (12.3)]*.
Pimozide and thioridazine are contraindicated for use with fluoxetine. Avoid the concomitant use of drugs known to prolong the QT interval. These include specific antipsychotics (e.g., ziprasidone, iloperidone, chlorpromazine, mesoridazine, droperidol); specific antibiotics (e.g.,erythromycin, gatifloxacin, moxifloxacin, sparfloxacin); Class 1A antiarrhythmic medications (e.g., quinidine, procainamide); Class III antiarrhythmics (e.g., amiodarone, sotalol); and others (e.g., pentamidine, levomethadyl acetate, methadone, halofantrine, mefloquine, dolasetron mesylate, probucol or tacrolimus) *[see Drug Interactions (7.6, 7.7) and Clinical Pharmacology (12.3)]*.
Consider ECG assessment and periodic ECG monitoring if initiating treatment with fluoxetine in patients with risk factors for QT prolongation and ventricular arrhythmia. Consider discontinuing fluoxetine and obtaining a cardiac evaluation if patients develop signs or symptoms consistent with ventricular arrhythmia.

5.12 Use in Patients with Concomitant Illness
Clinical experience with fluoxetine in patients with concomitant systemic illness is limited. Caution is advisable in using fluoxetine in patients with diseases or conditions that could affect metabolism or hemodynamic responses.
Cardiovascular **-** 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 clinical studies during the product's premarket testing. However, the ECGs of 312 patients who received fluoxetine in double-blind trials were retrospectively evaluated; no conduction abnormalities that resulted in heart block were observed. The mean heart rate was reduced by approximately 3 beats/min.
Glycemic Control - 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.

5.13 Potential for Cognitive and Motor Impairment
As with any CNS-active drug, fluoxetine has the potential to impair judgment, thinking, or motor skills. Patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that the drug treatment does not affect them adversely.

5.14 Long Elimination Half-Life
Because of the long elimination half-lives of the parent drug and its major active metabolite, changes in dose will not be fully reflected in plasma for several weeks, affecting both strategies for titration to final dose and withdrawal from treatment. This is of potential consequence when drug discontinuation is required or when drugs are prescribed that might interact with fluoxetine and norfluoxetine following the discontinuation of fluoxetine *[see Clinical Pharmacology (12.3)]*.

5.15 Discontinuation Adverse Reactions
During marketing of fluoxetine, SNRIs, and SSRIs, there have been spontaneous reports of adverse reactions occurring upon discontinuation of these drugs, particularly when abrupt, including the following: dysphoric mood, irritability, agitation, dizziness, sensory disturbances (e.g., paresthesias such as electric shock sensations), anxiety, confusion, headache, lethargy, emotional lability, insomnia, and hypomania. While these reactions are generally self-limiting, there have been reports of serious discontinuation symptoms. Patients should be monitored for these symptoms when discontinuing treatment with fluoxetine. A gradual reduction in the dose rather than abrupt cessation is recommended whenever possible. If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, then resuming the previously prescribed dose may be considered. Subsequently, the physician may continue decreasing the dose but at a more gradual rate. Plasma fluoxetine and norfluoxetine concentration decrease gradually at the conclusion of therapy which may minimize the risk of discontinuation symptoms with this drug.

5.16 Sexual Dysfunction
Use of SSRIs, including fluoxetine, may cause symptoms of sexual dysfunction [see Adverse Reactions (6.1)]. In male patients, SSRI use may result in ejaculatory delay or failure, decreased libido, and erectile dysfunction. In female patients, SSRI use may result in decreased libido and delayed or absent orgasm.
It is important for prescribers to inquire about sexual function prior to initiation of fluoxetine and to inquire specifically about changes in sexual function during treatment, because sexual function may not be spontaneously reported. When evaluating changes in sexual function, obtaining a detailed history (including timing of symptom onset) is important because sexual symptoms may have other causes, including the underlying psychiatric disorder. Discuss potential management strategies to support patients in making informed decisions about treatment.

6 ADVERSE REACTIONS
The following adverse reactions are discussed in more detail in other sections of the labeling:
- Suicidal Thoughts and Behaviors in Children, Adolescents, and Young Adults *[see Boxed Warning and Warnings and Precautions (5.1)]*
- Serotonin Syndrome *[see Warnings and Precautions (5.2)]*
- Allergic Reactions and Rash *[see Warnings and Precautions (5.3)]*
- Screening Patients for Bipolar Disorder and Monitoring for Mania/Hypomania *[see Warnings and Precautions (5.4)]*
- Seizures *[see Warnings and Precautions (5.5)]*
- Altered Appetite and Weight *[see Warnings and Precautions (5.6)]*
- Increased Risk of Bleeding *[see Warnings and Precautions (5.7)]*
- Angle-closure Glaucoma *[see Warnings and Precautions (5.8)]*
- Hyponatremia *[see Warnings and Precautions (5.9)]*
- Anxiety and Insomnia *[see Warnings and Precautions (5.10)]*
- QT Prolongation *[see Warnings and Precautions (5.11)]*
- Potential for Cognitive and Motor Impairment *[see Warnings and Precautions (5.13)]*
- Discontinuation Adverse Reactions *[see Warnings and Precautions (5.15)]*

6.1 Clinical Trials Experience
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect or predict the rates observed in practice.
Multiple doses of fluoxetine have been administered to 10,782 patients with various diagnoses in US clinical trials. In addition, there have been 425 patients administered fluoxetine in panic clinical trials. The stated frequencies represent the proportion of individuals who experienced, at least once, an adverse reaction of the type listed. An adverse reaction was included if it occurred for the first time or worsened while receiving therapy following baseline evaluation.
Incidence in MDD, OCD, Bulimia, and Panic Disorder placebo-controlled clinical trials (excluding data from extensions of trials)-Table 2 enumerates the most common adverse reactions associated with the use of fluoxetine (incidence of at least 5% for fluoxetine and at least twice that for placebo within at least 1 of the indications) for the treatment of MDD, OCD, and bulimia in US controlled clinical trials and Panic Disorder in US plus non-US controlled trials. *Table 3* provides combined data for the pool of studies that are provided separately by indication in *Table 2*.

Table 2: Most Common Adverse Reactions: Incidence in Major Depressive Disorder, Obsessive Compulsive Disorder, Bulimia, and Panic Disorder Placebo-controlled Clinical Trials

	Percentage of Patients Reporting Event							
	MDD		OCD		Bulimia		Panic Disorder	
Body System / Adverse Reaction	**Fluoxetine** (N=1,728)	**Placebo** (N=975)	**Fluoxetine** (N=266)	**Placebo** (N=89)	**Fluoxetine** (N=450)	**Placebo** (N=267)	**Fluoxetine** (N=425)	**Placebo**
Body as a Whole								
Asthenia	9	5	15	11	21	9	7	7
Flu Syndrome	3	4	10	7	8	3	5	5
Cardiovascular System								
Vasodilatation	3	2	5	--	2	1	1	--
Digestive System								
Nausea	21	9	26	13	29	11	12	7
Diarrhea	12	8	18	13	8	6	9	4
Anorexia	11	2	17	10	8	4	4	1
Dry mouth	10	7	12	3	9	6	4	4
Dyspepsia	7	5	10	4	10	6	6	2
Nervous System								
Insomnia	16	9	28	22	33	13	10	7
Anxiety	12	7	14	7	15	9	6	2
Nervousness	14	9	14	15	11	5	8	6
Somnolence	13	6	17	7	13	5	5	2
Tremor	10	3	9	1	13	1	3	1
Libido decreased	3	--	11	2	5	1	1	2
Abnormal dreams	1	1	5	2	5	3	1	1
Respiratory System								
Pharyngitis	3	3	11	9	10	5	3	3
Sinusitis	1	4	5	2	6	4	2	3
Yawn	--	--	7	--	11	--	1	--
Skin and Appendages								
Sweating	8	3	7	--	8	3	2	2
Rash	4	3	6	3	4	4	2	2
Urogenital System								
Impotence‡	2	--	--	--	7	--	1	--
Abnormal ejaculation‡	--	--	7	--	7	--	2	1

Note: Includes US data for MDD, OCD, Bulimia, and Panic Disorder clinical trials, plus non-US data for Panic Disorder clinical trials.
‡ = Denominator used was for males only (N=690 fluoxetine MDD; N=410 placebo MDD; N=116 fluoxetine OCD; N=43 placebo OCD; N=14 fluoxetine Bulimia; N=1 placebo Bulimia; N=162 fluoxetine Panic Disorder; N=121 placebo Panic Disorder).
-- = Incidence less than 1%.

Table 3: Adverse Reactions: Incidence in Major Depressive Disorder, Obsessive Compulsive Disorder, Bulimia, and Panic Disorder Placebo-controlled Clinical Trials

	Percentage of Patients Reporting Event	
	MDD, OCD, Bulimia, and Panic Disorder Combined	
Body System/ Adverse Reaction	**Fluoxetine (N=2,869)**	**Placebo (N=1,673)**
Body as a Whole		
Headache	21	19
Asthenia	11	6
Flu syndrome	5	4
Fever	2	1
Cardiovascular System		
Vasodilatation	2	1
Digestive System		
Nausea	22	9
Diarrhea	11	7
Anorexia	10	3
Dry mouth	9	6
Dyspepsia	8	4
Constipation	5	4
Flatulence	3	2
Vomiting	3	2
Metabolic and Nutritional Disorders		
Weight loss	2	1
Nervous System		
Insomnia	19	10
Nervousness	13	8
Anxiety	12	6
Somnolence	12	5
Dizziness	9	6
Tremor	9	2
Libido decreased	4	1
Thinking abnormal	2	1
Respiratory System		
Yawn	3	--
Skin and Appendages		
Sweating	7	3
Rash	4	3
Pruritus	3	2
Special Senses		
Abnormal vision	2	1

Note: Includes US data for MDD, OCD, Bulimia, and Panic Disorder clinical trials, plus non-US data for Panic Disorder clinical trials.
-- = Incidence less than 1%.
Associated with discontinuation in MDD, OCD, Bulimia, and Panic Disorder placebo-controlled clinical trials (excluding data from extensions of trials)-Table 4 lists the adverse reactions 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 reaction associated with discontinuation) in MDD, OCD, Bulimia, and Panic Disorder clinical trials, plus non-US Panic Disorder clinical trials.

Table 4: Most Common Adverse Reactions Associated with Discontinuation in Major Depressive Disorder, Obsessive Compulsive Disorder, Bulimia, and Panic Disorder Placebo-Controlled Clinical Trials

MDD, OCD, Bulimia, and Panic Disorder Combined (N=1,533)	**MDD** (N=392)	**OCD** (N=266)	**Bulimia** (N=450)	**Panic Disorder** (N=425)
Anxiety (1%)	--	Anxiety (2%)	--	Anxiety (2%)
--	--	--	Insomnia (2%)	--
--	Nervousness (1%)	--	--	Nervousness (1%)
--	--	Rash (1%)	--	--

Note: Includes US data for MDD, OCD, Bulimia, and Panic Disorder clinical trials, plus non-US data for Panic Disorder clinical trials.
-- = Incidence less than 1%.
Other adverse reactions in pediatric patients (children and adolescents)-Adverse reactions were collected in 322 pediatric patients (180 fluoxetine-treated, 142 placebo-treated). The overall profile of adverse reactions was generally similar to that seen in adult studies, as shown in *Table 2* and *Table 3*. However, the following adverse reactions (excluding those which appear in the body or footnotes of *Table 2* and *Table 3* and those for which the COSTART terms were uninformative or misleading) were reported at an incidence of at least 2% for fluoxetine and greater than placebo: thirst, hyperkinesia, agitation, personality disorder, epistaxis, urinary frequency, and menorrhagia.
The most common adverse reaction (incidence at least 1% for fluoxetine and greater than placebo) associated with discontinuation in 3 pediatric placebo-controlled trials (N=418 randomized; 228 fluoxetine-treated; 190 placebo-treated) was mania/hypomania (1.8% for fluoxetine-treated, 0% for placebo-treated). In these clinical trials, only a primary reaction associated with discontinuation was collected.
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 physicians 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 US MDD, OCD, and bulimia placebo-controlled clinical trials, decreased libido was the only sexual adverse reaction 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 persist after discontinuation of fluoxetine treatment.
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, physicians should routinely inquire about such possible adverse reactions.
Other adverse reactions observed during the premarketing evaluation of fluoxetine—Following is a list of adverse reactions reported by patients treated with fluoxetine in clinical trials. This listing is not intended to include reactions (1) already listed in previous tables or elsewhere in labeling, (2) for which a drug cause was remote, (3) which were so general as to be uninformative, (4) which were not considered to have significant clinical implications, or (5) which occurred at a rate equal to or less than placebo.
Reactions are classified by body system using the following definitions: frequent adverse reactions are those occurring in at least 1/100 patients; infrequent adverse reactions are those occurring in 1/100 to 1/1000 patients; rare reactions are those occurring in fewer than 1/1000 patients.
Body as a Whole—*Frequent*: chills; *Infrequent:* suicide attempt; *Rare:* acute abdominal syndrome, photosensitivity reaction.
Cardiovascular System—*Frequent:* palpitation; *Infrequent:* arrhythmia, hypotension[1].
Digestive System—*Infrequent:* dysphagia, gastritis, gastroenteritis, melena, stomach ulcer; *Rare:* bloody diarrhea, duodenal

9.125”
17.0” W
.625”
.625”
6.625”
Width: 17.0”
Length: 18.75”
Fold: 1.25” x 1.25”
422-02-2024
FLUOXETINE TABLETS
60 MG
1.25”H x 1.25”W
18.75”L

ulcer, esophageal ulcer, gastrointestinal hemorrhage, hematemesis, hepatitis, peptic ulcer, stomach ulcer hemorrhage.

Hemic and Lymphatic System—*Infrequent:* ecchymosis; *Rare:* petechia, purpura.

Nervous System—*Frequent:* emotional lability; *Infrequent:* akathisia, ataxia, balance disorder[1], bruxism[1], buccoglossal syndrome, depersonalization, euphoria, hypertonia, libido increased, myoclonus, paranoid reaction; *Rare:* delusions.

Respiratory System—*Rare:* larynx edema.

Skin and Appendages—*Infrequent:* alopecia; *Rare:* purpuric rash.

Special Senses—*Frequent:* taste perversion; *Infrequent:* mydriasis.

Urogenital System—*Frequent:* micturition disorder; *Infrequent:* dysuria, gynecological bleeding[2].

[1] MedDRA dictionary term from integrated database of placebo controlled trials of 15,870 patients, of which 9,673 patients received fluoxetine.

[2] Group term that includes individual MedDRA terms: cervix hemorrhage uterine, dysfunctional uterine bleeding, genital hemorrhage, menometrorrhagia, menorrhagia, metrorrhagia, polymenorrhea, postmenopausal hemorrhage, uterine hemorrhage, vaginal hemorrhage. Adjusted for gender.

6.2 Postmarketing Experience

The following adverse reactions have been identified during postapproval use of fluoxetine. Because these reactions are reported voluntarily from a population of uncertain size, it is difficult to reliably estimate their frequency or evaluate a causal relationship to drug exposure.

Voluntary reports of adverse reactions temporally associated with fluoxetine that have been received since market introduction and that may have no causal relationship with the drug include the following: anosmia, aplastic anemia, atrial fibrillation[1], cataract, cerebrovascular accident[1], cholestatic jaundice, drug reaction with eosinophilia and systemic symptoms (DRESS), 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[1], epidermal necrolysis, erythema multiforme, erythema nodosum, exfoliative dermatitis, galactorrhea, gynecomastia, heart arrest[1], hepatic failure/necrosis, hyperprolactinemia, hypoglycemia, hyponatremia, immune-related hemolytic anemia, immune-related hemolytic anemia, kidney failure, memory impairment, movement disorders developing in patients with risk factors including drugs associated with such reactions and worsening of pre-existing movement disorders, optic neuritis, pancreatitis[1], pancytopenia, pulmonary embolism, pulmonary hypertension, QT prolongation, Stevens-Johnson syndrome, thrombocytopenia[1], thrombocytopenic purpura, ventricular tachycardia (including Torsades de Pointes– type arrhythmias), vaginal bleeding, and violent behaviors[1].

[1] These terms represent serious adverse events, but do not meet the definition for adverse drug reactions. They are included here because of their seriousness.

7 DRUG INTERACTIONS

As with all drugs, the potential for interaction by a variety of mechanisms (e.g., pharmacodynamic, pharmacokinetic drug inhibition or enhancement, etc.) is a possibility.

7.1 Monoamine Oxidase Inhibitors (MAOIs)

[See Dosage and Administration (2.6, 2.7), Contraindications (4.1), and Warnings and Precautions (5.2)].

7.2 CNS Acting Drugs

Caution is advised if the concomitant administration of fluoxetine and such drugs is required. In evaluating individual cases, consideration should be given to using lower initial doses of the concomitantly administered drugs, using conservative titration schedules, and monitoring of clinical status *[see Clinical Pharmacology (12.3)].*

7.3 Other Serotonergic Drugs

The concomitant use of serotonergic drugs (including other SSRIs, SNRIs, triptans, tricyclic antidepressants, opioids, lithium, buspirone, amphetamines, tryptophan, and St. John's Wort) with fluoxetine increases the risk of serotonin syndrome. Monitor patients for signs and symptoms of serotonin syndrome, particularly during treatment initiation and dosage increases. If serotonin syndrome occurs, consider discontinuation of fluoxetine and/or concomitant serotonergic drugs *[see Warnings and Precautions (5.2)].*

7.4 Drugs that Interfere with Hemostasis (e.g., NSAIDS, Aspirin, Warfarin)

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 or aspirin may potentiate this risk of bleeding. Altered anticoagulant effects, including increased bleeding, have been reported when SNRIs or SSRIs are coadministered with warfarin. Patients receiving warfarin therapy should be carefully monitored when fluoxetine is initiated or discontinued *[see Warnings and Precautions (5.7)].*

7.5 Potential for Other Drugs to Affect Fluoxetine

Drugs tightly bound to plasma proteins-Because fluoxetine is tightly bound to plasma proteins, adverse effects may result from displacement of protein-bound fluoxetine by other tightly-bound drugs *[see Clinical Pharmacology (12.3)].*

7.6 Potential for Fluoxetine to Affect Other Drugs

Pimozide-Concomitant use in patients taking pimozide is contraindicated. Pimozide can prolong the QT interval. Fluoxetine can increase the level of pimozide through inhibition of CYP2D6. Fluoxetine can also prolong the QT interval. Clinical studies of pimozide with other antidepressants demonstrate an increase in drug interaction or QT prolongation. While a specific study with pimozide and fluoxetine has not been conducted, the potential for drug interactions or QT prolongation warrants restricting the concurrent use of pimozide and fluoxetine *[see Contraindications (4.2), Warnings and Precautions (5.11), and Drug Interactions (7.7)].*

Thioridazine-Thioridazine should not be administered with fluoxetine or within a minimum of 5 weeks after fluoxetine has been discontinued, because of the risk of QT Prolongation *[see Contraindications (4.2), Warnings and Precautions (5.11), and Drug Interactions (7.7)].*

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 C_{max} and a 4.5-fold higher area under the curve (AUC) for thioridazine in the slow hydroxylators compared with the rapid hydroxylators. The rate of debrisoquin hydroxylation is felt to depend on the level of CYP2D6 isozyme activity. Thus, this study suggests that drugs which inhibit CYP2D6, such as certain SSRIs, including fluoxetine, will produce elevated plasma levels of thioridazine.

Thioridazine administration produces a dose-related prolongation of the QT 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.

Drugs metabolized by CYP2D6-Fluoxetine inhibits the activity of CYP2D6, and may make individuals with normal CYP2D6 metabolic activity resemble a poor metabolizer. Co-administration of fluoxetine with other drugs that are metabolized by CYP2D6, including certain antidepressants (e.g., TCAs), antipsychotics (e.g., phenothiazines and most atypicals), and antiarrhythmics (e.g., propafenone, flecainide, and others) should be approached with caution. Therapy with medications that are predominantly metabolized by the CYP2D6 system and that have a relatively narrow therapeutic index (see list below) 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. Thus, his/her dosing requirements resemble those of poor metabolizers. If fluoxetine is added to the treatment regimen of a patient already receiving a drug metabolized by CYP2D6, the need for decreased dose of the original medication should be considered. Drugs with a narrow therapeutic index represent the greatest concern (e.g., flecainide, propafenone, vinblastine, and TCAs). Due to the risk of serious ventricular arrhythmias and sudden death potentially associated with elevated plasma levels of thioridazine, thioridazine should not be administered with fluoxetine or within a minimum of 5 weeks after fluoxetine has been discontinued *[see Contraindications (4.2)].*

Tricyclic Antidepressants (TCAs)-In 2 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 3 weeks or longer after fluoxetine is discontinued. Thus, the dose of TCAs may need to be reduced and plasma TCA concentrations may need to be monitored temporarily when fluoxetine is co-administered or has been recently discontinued *[see Warnings and Precautions (5.2) and Clinical Pharmacology (12.3)].*

Benzodiazepines-The half-life of concurrently administered diazepam may be prolonged in some patients *[see Clinical Pharmacology (12.3)].* Co-administration of alprazolam and fluoxetine has resulted in increased alprazolam plasma concentrations and in further psychomotor performance decrement due to increased alprazolam levels.

Antipsychotics-Some clinical data suggests a possible pharmacodynamic and/or pharmacokinetic interaction between SSRIs and antipsychotics. Elevation of blood levels of haloperidol and clozapine has been observed in patients receiving concomitant fluoxetine.

Anticonvulsants-Patients on stable doses of phenytoin and carbamazepine have developed elevated plasma anticonvulsant concentrations and clinical anticonvulsant toxicity following initiation of concomitant fluoxetine treatment.

Lithium-There have been reports of both increased and decreased lithium levels when lithium was used concomitantly with fluoxetine. Cases of lithium toxicity and increased serotonergic effects have been reported. Lithium levels should be monitored when these drugs are administered concomitantly *[see Warnings and Precautions (5.2)].*

Drugs tightly bound to plasma proteins-Because fluoxetine is tightly bound to plasma proteins, the administration of fluoxetine to a patient taking another drug that is tightly bound to protein (e.g., Coumadin, digitoxin) may cause a shift in plasma concentrations potentially resulting in an adverse effect *[see Clinical Pharmacology (12.3)].*

Drugs Metabolized by CYP3A4-In an *in vivo* interaction study involving co-administration of fluoxetine with single doses of terfenadine (a CYP3A4 substrate), no increase in plasma terfenadine concentrations occurred with concomitant fluoxetine.

Additionally, in vitro studies have shown ketoconazole, a potent inhibitor of CYP3A4 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 CYP3A4 activity is not likely to be of clinical significance.

Olanzapine-Fluoxetine (60-mg single dose or 60-mg daily dose for 8 days) causes a small (mean 16%) increase in the maximum concentration of olanzapine and a small (mean 16%) decrease in olanzapine clearance. The magnitude of the impact of this factor is small in comparison to the overall variability between individuals, and therefore dose modification is not routinely recommended.

7.7 Drugs that Prolong the QT Interval

Do not use fluoxetine in combination with thioridazine or pimozide. Use fluoxetine with caution in combination with other drugs that cause QT prolongation. These include: specific antipsychotics (e.g., ziprasidone, iloperidone, chlorpromazine, mesoridazine, droperidol); specific antibiotics (e.g., erythromycin, gatifloxacin, moxifloxacin, sparfloxacin); Class IA antiarrhythmic medications (e.g., quinidine, procainamide); Class III antiarrhythmics (e.g., amiodarone, sotalol); and others (e.g., pentamidine, levomethadyl acetate, methadone, halofantrine, mefloquine, dolasetron mesylate, probucol or tacrolimus). Fluoxetine is primarily metabolized by CYP2D6. Concomitant treatment with CYP2D6 inhibitors can increase the concentration of fluoxetine. Concomitant use of other highly protein-bound drugs can increase the concentration of fluoxetine *[see Contraindications (4.2), Warnings and Precautions (5.11), Drug Interactions (7.6), and Clinical Pharmacology (12.3)].*

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to antidepressants during pregnancy. Healthcare providers are encouraged to register patients by calling the National Pregnancy Registry for Antidepressants at 1-866-961-2388 or visiting online at

https://womensmentalhealth.org/research/pregnancyregistry/antidepressants/.

Risk Summary

Based on data from published observational studies, exposure to SSRIs, particularly in the month before delivery, has been associated with a less than 2-fold increase in the risk of postpartum hemorrhage *[see Warnings and Precautions (5.7) and Clinical Considerations].*

Available data from published epidemiologic studies and postmarketing reports over several decades have not established an increased risk of major birth defects or miscarriage. Some studies have reported an increased incidence of cardiovascular malformations; however, these studies results do not establish a causal relationship *[see Data].* There are risks associated with untreated depression in pregnancy and risks of persistent pulmonary hypertension of the newborn (PPHN) *(see Data)* and poor neonatal adaptation with exposure to selective serotonin reuptake inhibitors (SSRIs), including Fluoxetine Tablets, during pregnancy *(see Clinical Considerations).*

In rats and rabbits treated with fluoxetine during the period of organogenesis, there was no evidence of developmental effects at doses up to 1.6 times and 3.9 times, respectively, the maximum recommended human dose (MRHD) of 60 mg on a mg/m^2 given to adolescents on a mg/m^2 basis. However, in other reproductive studies in rats, an increase in stillborn pups, a decrease in pup weight, and an increase in pup deaths early after birth occurred at doses that are 1.5 times (during gestation) and 0.97 times (during gestation and lactation) the MRHD given to adolescents on a mg/m^2 basis.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the US general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Clinical Considerations

Disease-Associated Maternal and/or Embryo/Fetal Risk

Women who discontinue antidepressants during pregnancy are more likely to experience a relapse of major depression than women who continue antidepressants. This finding is from a prospective, longitudinal study that followed 201 pregnant women with a history of major depressive disorder who were euthymic and taking antidepressants at the beginning of pregnancy. Consider the risk of untreated depression when discontinuing or changing treatment with antidepressant medication during pregnancy and postpartum.

Maternal Adverse Reactions

Use of Fluoxetine Tablets in the month before delivery may be associated with an increased risk of postpartum hemorrhage *[see Warnings and Precautions (5.7)].*

Fetal/Neonatal Adverse Reactions

Neonates exposed to Fluoxetine Tablets and other SSRIs or SNRIs 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, tremors, jitteriness, irritability, and constant crying. These findings are consistent with either a direct toxic effect of SSRIs and SNRIs or possibly a drug discontinuation syndrome. It should be noted that, in some cases, the clinical picture is consistent with serotonin syndrome *[see Warnings and Precautions (5.2)].*

Data

Human Data

It has been shown that SSRIs (including fluoxetine) can cross the placenta. Published epidemiological studies of pregnant women exposed to fluoxetine have not established an increased risk of major birth defects, miscarriage, and other adverse developmental outcomes. Several publications reported an increased incidence of cardiovascular malformations in children with in utero exposure to fluoxetine. However, these studies results do not establish a causal relationship. Methodologic limitations of these observational studies include possible exposure and outcome misclassification, lack of adequate controls, adjustment for confounders and confirmatory studies. However, these studies cannot definitely establish or exclude any drug-associated risk during pregnancy.

Exposure to SSRIs, particularly later in pregnancy, may have an increased risk for PPHN. PPHN occurs in 1 to 2 per 1000 live births in the general population and is associated with substantial neonatal morbidity and mortality.

Animal data

In embryofetal development studies in rats and rabbits, there was no evidence of malformations or developmental variations following administration of fluoxetine at doses up to 12.5 and 15 mg/kg/day, respectively (1.6 and 3.9 times, respectively, the MRHD of 60 mg given to adolescents on a mg/m^2 basis) throughout organogenesis. However, in rat reproduction studies, an increase in stillborn pups, a decrease in pup weight, and an increase in pup deaths during the first 7 days postpartum occurred following maternal exposure to 12 mg/kg/day (1.5 times the MRHD given to adolescents on a mg/m^2 basis) during gestation or 7.5 mg/kg/day (0.97 times the MRHD given to adolescents on a mg/m^2 basis) during gestation and lactation. There was no evidence of developmental neurotoxicity in the surviving offspring of rats treated with 12 mg/kg/day during gestation. The no-effect dose for rat pup mortality was 5 mg/kg/day (0.65 times the MRHD given to adolescents on a mg/m^2 basis).

8.2 Lactation

Risk Summary

Data from published literature report the presence of fluoxetine and norfluoxetine in human milk *(see Data).* There are reports of agitation, irritability, poor feeding, and poor weight gain in infants exposed to fluoxetine through breast milk *(see Clinical Considerations).* There are no data on the effect of fluoxetine or its metabolites on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Fluoxetine Tablets and any potential adverse effects on the breastfed child from Fluoxetine Tablets or the underlying maternal condition.

Clinical Considerations

Infants exposed to Fluoxetine Tablets should be monitored for agitation, irritability, poor feeding, and poor weight gain.

Data

A study of 19 nursing mothers on fluoxetine with daily doses of 10 mg to 60 mg showed that fluoxetine was detectable in 30% of nursing infant sera (range: 1 to 84 ng/mL) whereas norfluoxetine was found in 85% (range: <1 to 265 ng/mL).

8.4 Pediatric Use

Use of fluoxetine *in children*-The efficacy of fluoxetine for the treatment of MDD was demonstrated in two 8- to 9-week placebo-controlled clinical trials with 315 pediatric outpatients ages 8 to ≤ 18 *[see Clinical Studies (14.1)].*

The efficacy of fluoxetine for the treatment of OCD was demonstrated in one 13-week placebo-controlled clinical trial with 103 pediatric outpatients ages 7 to < 18 *[see Clinical Studies (14.2)].*

The safety and effectiveness in pediatric patients < 8 years of age in MDD and < 7 years of age in OCD have not been established.

Fluoxetine pharmacokinetics were evaluated in 21 pediatric patients (ages 6 to ≤ 18) with MDD or OCD *[see Clinical Pharmacology (12.3)].*

The acute adverse reaction profiles observed in the 3 studies (N=418 randomized; 228 fluoxetine-treated, 190 placebo-treated) were generally similar to that observed in adult studies with fluoxetine. The longer-term adverse reaction profile observed in the 19-week MDD study (N=219 randomized; 109 fluoxetine-treated, 110 placebo-treated) was also similar to that observed in adult trials with fluoxetine *[see Adverse Reactions (6.1)].*

Manic reaction, including mania and hypomania, was reported in 6 (1 mania, 5 hypomania) out of 228 (2.6%) fluoxetine-treated patients and in 0 out of 190 (0%) placebo-treated patients. Mania/hypomania led to the discontinuation of 4 (1.8%) fluoxetine-treated patients from the acute phases of the 3 studies combined. Consequently, regular monitoring for the occurrence of mania/hypomania is recommended.

As with other SSRIs, decreased weight gain has 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 gained an average of 1.1 cm less in height and 1.1 kg less in weight than subjects treated with placebo. In addition, fluoxetine treatment was associated with a decrease in alkaline phosphatase levels. The safety of fluoxetine treatment for pediatric patients has not been systematically assessed for chronic treatment longer than several months in duration. In particular, there are no studies that directly evaluate the longer-term effects of fluoxetine on the growth, development, and maturation of children and adolescent patients. Therefore, height and weight should be monitored periodically in pediatric patients receiving fluoxetine. *[see Warnings and Precautions (5.6)].*

Fluoxetine is approved for use in pediatric patients with MDD and OCD *[see Boxed Warning and Warnings and Precautions (5.1)]*. Anyone considering the use of fluoxetine in a child or adolescent must balance the potential risks with the clinical need.

Juvenile Animal Toxicity Data-Significant toxicity on muscle tissue, neurobehavior, reproductive organs, and bone development has been observed following exposure of juvenile rats to fluoxetine from weaning through maturity. Oral administration of fluoxetine to rats from weaning postnatal day 21 through adulthood day 90 at 3 mg/kg/day, 10 mg/kg/day, or 30 mg/kg/day was associated with testicular degeneration and necrosis, epididymal vacuolation, and hypospermia (at 30 mg/kg/day corresponding to plasma exposures [AUC] approximately 5 to 10 times the average AUC in pediatric patients at the MRHD of 20 mg/day); increased serum levels of creatine kinase (at AUC as low as 1 to 2 times the average AUC in pediatric patients at the MRHD of 20 mg/day); skeletal muscle degeneration and necrosis; decreased femur length/growth; and body weight gain (at AUC 5 to10 times the average AUC in pediatric patients at the MRHD of 20 mg/day). The high dose of 30 mg/kg/day exceeded a maximum tolerated dose. When animals were evaluated after a drug-free period (up to 11 weeks after cessation of dosing), fluoxetine was associated with neurobehavioral abnormalities (decreased reactivity at AUC as low as approximately 0.1 to 0.2 times the average AUC in pediatric patients at the MRHD and learning deficit at the high dose) and reproductive functional impairment (decreased mating at all doses and impaired fertility at the high dose). In addition, the testicular and epididymal microscopic lesions and decreased sperm concentrations found in the high dose group were also observed, indicating that the drug effects on reproductive organs are irreversible. The reversibility of fluoxetine-induced muscle damage was not assessed.

These fluoxetine toxicities in juvenile rats have not been observed in adult animals. Plasma exposures (AUC) to fluoxetine in juvenile rats receiving 3 mg/kg/day, 10 mg/kg/day, or 30 mg/kg/day doses in this study are approximately 0.1 to 0.2, 1 to 2, and 5 to 10 times, respectively, the average exposure in pediatric patients receiving the MRHD of 20 mg/day. Rat exposures to the major metabolite, norfluoxetine, were approximately 0.3 to 0.8, 1 to 8, and 3 to 20 times, respectively, the pediatric exposure at the MRHD.

A specific effect on bone development was reported in juvenile mice administered fluoxetine by the intraperitoneal route to 4-week-old mice for 4 weeks at doses 0.5 and 2 times the oral MRHD of 20 mg/day on a mg/m^2 basis. There was a decrease in bone mineralization and density at both doses, but the overall growth (body weight gain or femur length) was not affected.

8.5 Geriatric Use

US fluoxetine clinical trials included 687 patients ≥ 65 years of age and 93 patients ≥ 75 years of age. The efficacy in geriatric patients has been established *[see Clinical Studies (14.1)]*. For pharmacokinetic information in geriatric patients, *[see Clinical Pharmacology (12.3)]*. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out. SNRIs and SSRIs, including fluoxetine, have been associated with cases of clinically significant hyponatremia in elderly patients, who may be at greater risk for this adverse reaction *[see Warnings and Precautions (5.9)].*

8.6 Hepatic Impairment

In subjects with cirrhosis of the liver, the clearances of fluoxetine and its active metabolite, norfluoxetine, were decreased, thus increasing the elimination half-lives of these substances. A lower or less frequent dose of fluoxetine should be used in patients with cirrhosis. Caution is advised when using fluoxetine in patients with diseases or conditions that could affect its metabolism *[see Dosage and Administration (2.5) and Clinical Pharmacology (12.3)].*

9 DRUG ABUSE AND DEPENDENCE

9.3 Dependence

Fluoxetine has not been systematically studied, in animals or humans, for its potential for abuse, tolerance, or physical dependence. While the premarketing clinical experience with fluoxetine did not reveal any tendency for a withdrawal syndrome or any drug seeking behavior, these observations were not systematic and it is not possible to predict on the basis of this limited experience the extent to which a CNS active drug will be misused, diverted, and/or abused once marketed. Consequently, physicians should carefully evaluate patients for history of drug abuse and follow such patients closely, observing them for signs of misuse or abuse of fluoxetine (e.g., development of tolerance, incrementation of dose, drug-seeking behavior).

10 OVERDOSAGE

The following have been reported with fluoxetine tablet overdosage:

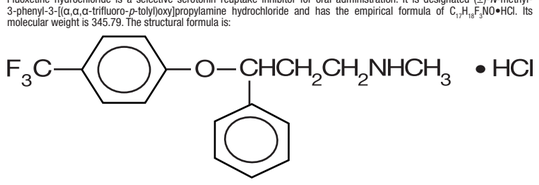
- Seizures, which may be delayed, and altered mental status including coma.
- Cardiovascular toxicity, which may be delayed, including QRS and QTc interval prolongation, wide complex tachyarrhythmias, torsade de pointes, and cardiac arrest. Hypertension most commonly seen, but rarely can see hypotension alone or with co-ingestants including alcohol.
- Serotonin syndrome (patients with a multiple drug overdosage with other pro serotonergic drugs may have a higher risk).

Gastrointestinal decontamination with activated charcoal should be considered in patients who present early after a fluoxetine overdose.

Consider contacting a Poison Center (1-800-221-2222) or a medical toxicologist for additional overdosage management recommendations.

11 DESCRIPTION

Fluoxetine hydrochloride is a selective serotonin reuptake inhibitor for oral administration. It is designated (±)-*N*-methyl-3-phenyl-3-[(α,α,α-trifluoro-*p*-tolyl)oxy]propylamine hydrochloride and has the empirical formula of $C_{17}H_{18}F_3NO$•HCl. Its molecular weight is 345.79. The structural formula is:



Fluoxetine hydrochloride, USP is a white to off-white crystalline powder with a solubility of 14 mg/mL in water.

Each scored tablet contains fluoxetine hydrochloride equivalent to 60 mg (194 µmol) of fluoxetine. In addition, each scored tablet also contains the following inactive ingredients: microcrystalline cellulose, corn starch (maize), povidone, mannitol, magnesium stearate, hypromellose, titanium dioxide and polyethylene glycol.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Although the exact mechanism of fluoxetine is unknown, it is presumed to be linked to its inhibition of CNS neuronal uptake of serotonin.

12.2 Pharmacodynamics

Studies at clinically relevant doses in man have demonstrated that fluoxetine blocks the uptake of serotonin into human platelets. Studies in animals also suggest that fluoxetine is a much more potent uptake inhibitor of serotonin than of norepinephrine. Antagonism of muscarinic, histaminergic, and α_1-adrenergic receptors has been hypothesized to be associated with various anticholinergic, sedative, and cardiovascular effects of classical TCA drugs. Fluoxetine binds to these and other membrane receptors from brain tissue much less potently in vitro than do the tricyclic drugs.

12.3 Pharmacokinetics

Systemic bioavailability-In man, following a single, oral dose of fluoxetine 60 mg tablet, USP, the peak plasma concentration of fluoxetine and time to achieve peak plasma concentration were 49.6 ± 10.0 ng/mL, and 7.20 ± 1.41 hours, respectively (both values are mean ± SD).

The capsule, tablet, and oral solution dosage forms of fluoxetine are bioequivalent. The exposure (C_{max}, AUC) to fluoxetine was similar after administration of either 1 × 60 mg fluoxetine tablet USP or 3 × 20 mg fluoxetine tablets. Food does not appear to affect the systemic bioavailability of fluoxetine, although it may delay its absorption by 1 to 2 hours, which is probably not clinically significant. Thus, fluoxetine may be administered with or without food.

Protein binding-Over the concentration range from 200 ng/mL to 1,000 ng/mL, approximately 94.5% of fluoxetine is bound in vitro to human serum proteins, including albumin and α_1-glycoprotein. The interaction between fluoxetine and other highly protein-bound drugs has not been fully evaluated, but may be important.

Enantiomers-Fluoxetine is a racemic mixture (50/50) of *R*-fluoxetine and *S*-fluoxetine enantiomers. In animal models, both enantiomers are specific and potent serotonin uptake inhibitors with essentially equivalent pharmacologic activity. The *S*-fluoxetine enantiomer is eliminated more slowly and is the predominant enantiomer present in plasma at steady state.

Metabolism-Fluoxetine is extensively metabolized in the liver to norfluoxetine and a number of other unidentified metabolites. The only identified active metabolite, norfluoxetine, is formed by demethylation of fluoxetine. In animal models, *S*-norfluoxetine is a potent and selective inhibitor of serotonin uptake and has activity essentially equivalent to *R*- or *S*-fluoxetine. *R*-norfluoxetine is significantly less potent than the parent drug in the inhibition of serotonin uptake. The primary route of elimination appears to be hepatic metabolism to inactive metabolites excreted by the kidney.

Variability in metabolism-A subset (about 7%) of the population has reduced activity of the drug metabolizing enzyme cytochrome P450 2D6 (CYP2D6). Such individuals are referred to as "poor metabolizers" of drugs such as debrisoquin, dextromethorphan, and the TCAs. In a study involving labeled and unlabeled enantiomers administered as a racemate, these individuals metabolized *S*-fluoxetine at a slower rate and thus achieved higher concentrations of *S*-fluoxetine. Consequently, concentrations of *S*-norfluoxetine at steady state were lower. The metabolism of *R*-fluoxetine in these poor metabolizers appears normal. When compared with normal metabolizers, the total sum at steady state of the plasma concentrations of the 4 active enantiomers was not significantly greater among poor metabolizers. Thus, the net pharmacodynamic activities were essentially the same. Alternative, nonsaturable pathways (non-2D6) also contribute to the metabolism of fluoxetine. This explains how fluoxetine achieves a steady-state concentration rather than increasing without limit.

Because fluoxetine's metabolism, like that of a number of other compounds including TCAs and other SSRIs, involves the CYP2D6 system, concomitant therapy with drugs also metabolized by this enzyme system (such as the TCAs) may lead to drug interactions *[see Drug Interactions (7.6)]*.

Accumulation and Slow Elimination-The relatively slow elimination of fluoxetine (elimination half-life of 1 to 3 days after acute administration and 4 to 6 days after chronic administration) and its active metabolite, norfluoxetine (elimination half-life of 4 to 16 days after acute and chronic administration), leads to significant accumulation of these active species in chronic use and delayed attainment of steady state, even when a fixed dose is used *[see Warnings and Precautions (5.14)]*. After 30 days of dosing at 40 mg/day, plasma concentrations of fluoxetine in the range of 91 ng/mL to 302 ng/mL and norfluoxetine in the range of 72 ng/mL to 258 ng/mL have been observed. Plasma concentrations of fluoxetine were higher than those predicted by single-dose studies, because fluoxetine's metabolism is not proportional to dose. Norfluoxetine, however, appears to have linear pharmacokinetics. Its mean terminal half-life after a single dose was 8.6 days and after multiple dosing was 9.3 days. Steady-state levels after prolonged dosing are similar to levels seen at 4 to 5 weeks.

The long elimination half-lives of fluoxetine and norfluoxetine assure that, even when dosing is stopped, active drug substance will persist in the body for weeks (primarily depending on individual patient characteristics, previous dosing regimen, and length of previous therapy at discontinuation). This is of potential consequence when drug discontinuation is required or when drugs are prescribed that might interact with fluoxetine and norfluoxetine following the discontinuation of fluoxetine.

Liver Disease-As might be predicted from its primary site of metabolism, liver impairment can affect the elimination of fluoxetine. The elimination half-life of fluoxetine was prolonged in a study of cirrhotic patients, with a mean of 7.6 days compared with the range of 2 to 3 days seen in subjects without liver disease; norfluoxetine elimination was also delayed, with a mean duration of 12 days for cirrhotic patients compared with the range of 7 to 9 days in normal subjects. This suggests that the use of fluoxetine in patients with liver disease must be approached with caution. If fluoxetine is administered to patients with liver disease, a lower or less frequent dose should be used *[see Dosage and Administration (2.5) and Use in Specific Populations (8.6)].*

Renal Disease-In depressed patients on dialysis (N=12), fluoxetine administered as 20 mg once daily for 2 months produced steady-state fluoxetine and norfluoxetine plasma concentrations comparable with those seen in patients with normal renal function. While the possibility exists that renally excreted metabolites of fluoxetine may accumulate to higher levels in patients with severe renal dysfunction, use of a lower or less frequent dose is not routinely necessary in renally impaired patients.

Geriatric pharmacokinetics-The disposition of single doses of fluoxetine in healthy elderly subjects (> 65 years of age) did not differ significantly from that in younger normal subjects. However, given the long half-life and nonlinear disposition of the drug, a single-dose study is not adequate to rule out the possibility of altered pharmacokinetics in the elderly, particularly if they have systemic illness or are receiving multiple drugs for concomitant diseases. The effects of age upon the metabolism of fluoxetine have been investigated in 260 elderly but otherwise healthy depressed patients (≥ 60 years of age) who received 20 mg fluoxetine for 6 weeks. Combined fluoxetine plus norfluoxetine plasma concentrations were 209.3 ng/mL ± 85.7 ng/mL at the end of 6 weeks. No unusual age-associated pattern of adverse reactions was observed in those elderly patients.

Pediatric pharmacokinetics (children and adolescents)-Fluoxetine pharmacokinetics were evaluated in 21 pediatric patients (10 children ages 6 to < 13, 11 adolescents ages 13 to < 18) diagnosed with MDD or OCD. Fluoxetine 20 mg/day was administered for up to 62 days. The average steady-state concentrations of fluoxetine in these children were 2-fold higher than in adolescents (171 ng/mL and 86 ng/mL, respectively). The average norfluoxetine steady-state concentrations in these children were 1.5-fold higher than in adolescents (195 ng/mL and 113 ng/mL, respectively). These differences can be almost entirely explained by differences in weight. No gender-associated difference in fluoxetine pharmacokinetics was observed. Similar ranges of fluoxetine and norfluoxetine plasma concentrations were observed in another study in 94 pediatric patients (ages 8 to < 18) diagnosed with MDD.

Higher average steady-state fluoxetine and norfluoxetine concentrations were observed in children relative to adults; however, these concentrations were within the range of concentrations observed in the adult population. As in adults, fluoxetine and norfluoxetine accumulated extensively following multiple oral dosing; steady-state concentrations were achieved within 3 to 4 weeks of daily dosing.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, and Impairment of Fertility

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

Mutagenesis-Fluoxetine and norfluoxetine have been shown to have no genotoxic effects based on the following assays: bacterial mutation assay, DNA repair assay in cultured rat hepatocytes, mouse lymphoma assay, and in vivo sister chromatid exchange assay in Chinese hamster bone marrow cells.

Impairment of Fertility-Two fertility studies conducted in adult rats at doses of up to 7.5 mg/kg/day and 12.5 mg/kg/day (approximately 0.9 and 1.5 times the MRHD on a mg/m^2 basis) indicated that fluoxetine had no adverse effects on fertility. However, adverse effects on fertility were seen when juvenile rats were treated with fluoxetine *[see Use in Specific Populations (8.4)].*

13.2 Animal Toxicology and/or Pharmacology

Phospholipids are increased in some tissues of mice, rats, and dogs given fluoxetine chronically. This effect is reversible after cessation of fluoxetine treatment. Phospholipid accumulation in animals has been observed with many cationic amphiphilic drugs, including fenfluramine, imipramine, and ranitidine. The significance of this effect in humans is unknown.

14 CLINICAL STUDIES

Efficacy for fluoxetine was established for the:

- Acute and maintenance treatment of MDD in adults, and children and adolescents (8 to 18 years) in 7 short-term and 2 long-term, placebo-controlled trials *[see Clinical Studies (14.1)].*
- Acute treatment of obsessions and compulsions in adults, and children and adolescents (7 to 17 years) with OCD in 3 short-term, placebo-controlled trials *[see Clinical Studies (14.2)].*
- Acute and maintenance treatment of binge-eating and vomiting behaviors in adult patients with moderate to severe Bulimia Nervosa in 3 short-term and 1 long-term, placebo-controlled trials *[see Clinical Studies (14.3)].*
- Acute treatment of Panic Disorder, with or without agoraphobia, in adult patients in 2 short-term, placebo-controlled trials *[see Clinical Studies (14.4)].*

14.1 Major Depressive Disorder

Daily Dosing

Adult-The efficacy of fluoxetine was studied in 5- and 6-week placebo-controlled trials with depressed adult and geriatric outpatients (≥ 18 years of age) whose diagnoses corresponded most closely to the DSM-III (currently DSM-IV) category of MDD. Fluoxetine was shown to be significantly more effective than placebo as measured by the Hamilton Depression Rating Scale (HAM-D). Fluoxetine was also significantly more effective than placebo on the HAM-D subscores for depressed mood, sleep disturbance, and the anxiety subfactor.

Two 6-week controlled studies (N=671, randomized) comparing fluoxetine 20 mg and placebo have shown fluoxetine 20 mg daily to be effective in the treatment of elderly patients (≥ 60 years of age) with MDD. In these studies, fluoxetine produced a significantly higher rate of response and remission as defined, respectively, by a 50% decrease in the HAM-D score and a total endpoint HAM-D score of ≤ 8. Fluoxetine was well tolerated and the rate of treatment discontinuations due to adverse reactions did not differ between flu