

Sertraline Hydrochloride  
Tablets, USP

#### HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use SERTRALINE HYDROCHLORIDE TABLETS safely and effectively. See full prescribing information for SERTRALINE HYDROCHLORIDE TABLETS.

SERTRALINE HYDROCHLORIDE tablets, for oral use

Initial U.S. Approval: 1991

**WARNING: SUICIDAL THOUGHTS AND BEHAVIORS**  
**See full prescribing information for complete boxed warning**

- Antidepressants increased the risk of suicidal thoughts and behaviors in pediatric and young adult patients (5.1)
- Closely monitor for clinical worsening and emergence of suicidal thoughts and behaviors (5.1)

#### RECENT MAJOR CHANGES

Warnings and Precautions, Sexual Dysfunction (5.11) 9/2021

#### INDICATIONS AND USAGE

Sertraline hydrochloride tablets are selective serotonin reuptake inhibitor (SSRI) indicated for the treatment of (1):

- Major depressive disorder (MDD)
- Obsessive-compulsive disorder (OCD)
- Panic disorder (PD)
- Post-traumatic stress disorder (PTSD)
- Social anxiety disorder (SAD)
- Premenstrual dysphoric disorder (PMDD)

#### DOSE AND ADMINISTRATION

Indication	Starting Dosage	Maximum Dosage
MDD (2.1)	50 mg per day	200 mg per day
OCD (2.1)	25 mg per day (ages 6–12) 50 mg per day (ages ≥ 13)	200 mg per day
PD, PTSD, SAD (2.1)	25 mg per day	200 mg per day
PMDD (2.2) continuous dosing	50 mg per day	150 mg per day
PMDD (2.2) intermittent dosing	50 mg per day during luteal phase only	100 mg per day during luteal phase only

- If inadequate response to starting dosage, titrate in 25–50 mg per day increments once weekly in MDD, OCD, PD, PTSD, and SAD (2.1)
- See Full Prescribing Information for titration in PMDD (2.2)
- Hepatic impairment:
  - Mild: Recommended starting and maximum dosage is half recommended dosage (2.4)

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**WARNING: SUICIDAL THOUGHTS AND BEHAVIORS**  
**Antidepressants increased the risk of suicidal thoughts and behavior in pediatric and young adult patients in short-term studies. Closely monitor all antidepressant-treated patients for clinical worsening, and for emergence of suicidal thoughts and behaviors [See Warnings and Precautions (5.1)].**

##### 1 INDICATIONS AND USAGE

Sertraline hydrochloride tablets are indicated for the treatment of the following [See Clinical Studies (14)]:

- Major depressive disorder (MDD)
- Obsessive-compulsive disorder (OCD)
- Panic disorder (PD)
- Posttraumatic stress disorder (PTSD)
- Social anxiety disorder (SAD)
- Premenstrual dysphoric disorder (PMDD)

##### 2 DOSAGE AND ADMINISTRATION

###### 2.1 Dosage in Patients with MDD, OCD, PD, PTSD, and SAD

The recommended initial dosage and maximum sertraline hydrochloride dosage in patients with MDD, OCD, PD, PTSD, and SAD are displayed in Table 1 below. A dosage of 25 mg or 50 mg per day is the initial therapeutic dosage.

For adults and pediatric patients, subsequent dosages may be increased in case of an inadequate response in 25 to 50 mg per day increments once a week, depending on tolerability, up to a maximum of 200 mg per day. Given the 24-hour elimination half-life of sertraline hydrochloride, the recommended interval between dose changes is one week.

Table 1: Recommended Daily Dosage of Sertraline Hydrochloride in Patients with MDD, OCD, PD, PTSD, and SAD		
Indication	Starting Dose	Therapeutic Range
<b>Adults</b>	50 mg	50-200 mg
	50 mg	
OCD	50 mg	
PD, PTSD, SAD	25 mg	
<b>Pediatric Patients</b>	25 mg	50-200 mg
	50 mg	

###### 2.2 Dosage in Patients with PMDD

The recommended starting sertraline hydrochloride dosage in adult women with PMDD is 50 mg per day. Sertraline hydrochloride may be administered either continuously (every day throughout the menstrual cycle) or intermittently (only during the luteal phase of the menstrual cycle, i.e., starting the daily dosage 14 days prior to the anticipated onset of menstruation and continuing through the onset of menses). Intermittent dosing would be repeated with each new cycle.

- When dosing continuously, patients not responding to a 50 mg dosage may benefit from dosage increases at 50 mg increments per menstrual cycle up to 150 mg per day.
- When dosing intermittently, patients not responding to a 50 mg dosage may benefit from increasing the dosage up to a maximum of 100 mg per day during the next menstrual cycle (and subsequent cycles) as follows: 50 mg per day during the first 3 days of dosing followed by 100 mg per day during the remaining days in the dosing cycle.

###### 2.3 Screen for Bipolar Disorder Prior to Starting Sertraline Hydrochloride

Prior to initiating treatment with sertraline hydrochloride or another antidepressant, screen patients for a personal or family history of bipolar disorder, mania, or hypomania [See Warnings and Precautions (5.4)].

###### 2.4 Dosage Modifications in Patients with Hepatic Impairment

Both the recommended starting dosage and therapeutic range in patients with mild hepatic impairment (Child Pugh scores 5 or 6) are half the recommended daily dosage [See Dosage and Administration (2.1, 2.2)]. The use of sertraline hydrochloride in patients with moderate (Child Pugh scores 7 to 9) or severe hepatic impairment (Child Pugh scores 10–15) is not recommended [See Use in Specific Populations (8.6), Clinical Pharmacology (12.3)].

###### 2.5 Switching Patients to or from a Monoamine Oxidase Inhibitor Antidepressant

At least 14 days must elapse between discontinuation of a monoamine oxidase inhibitor (MAOI) antidepressant and initiation of sertraline hydrochloride. In addition, at least 14 days must elapse after stopping sertraline hydrochloride before starting an MAOI antidepressant [See Contraindications (4), Warnings and Precautions (5.2)].

###### 2.6 Discontinuation of Treatment with Sertraline Hydrochloride

Adverse reactions may occur upon discontinuation of sertraline hydrochloride [See Warnings and Precautions (5.5)]. Gradually reduce the dosage rather than stopping sertraline hydrochloride abruptly whenever possible.

##### 3 DOSAGE FORMS AND STRENGTHS

25 mg tablets: Green colored film coated, modified capsule shaped tablets, one side debossed with "T" and "25" with functional score line in between and plain on the other side.

50 mg tablets: Blue colored film coated, modified capsule shaped tablets, one side debossed with "T" and "50" with functional score line in between and plain on the other side.

100 mg tablets: Light yellow colored film coated, modified capsule shaped tablets, one side debossed with "T" and "100" with functional score line in between and plain on the other side.

##### 4 CONTRAINDICATIONS

- Sertraline hydrochloride is contraindicated in patients:
- Taking, or within 14 days of stopping, MAOIs, including the MAOIs linezolid and intravenous methylene blue because of an increased risk of serotonin syndrome [See Warnings and Precautions (5.2), Drug Interactions (7.1)].
  - Taking pimozide [See Drug Interactions (7.1)].
  - With known hypersensitivity to sertraline (e.g., anaphylaxis, angioedema) [See Adverse Reactions (6.1, 6.2)].

##### 5 WARNINGS AND PRECAUTIONS

**5.1 Suicidal Thoughts and Behaviors in Pediatric and Young Adult Patients**

In pooled analyses of placebo-controlled trials of antidepressant drugs (SSRIs and other antidepressant classes) that included approximately 77,000 adult patients and over 4,400 pediatric patients, the incidence of suicidal thoughts and behaviors in pediatric and young adult patients was greater in antidepressant-treated patients than in placebo-treated patients. The drug-placebo differences in the number of cases of suicidal thoughts and behaviors per 1000 patients treated are provided in Table 2.

No suicides occurred in any of the pediatric studies. There were suicides in the adult studies, but the number was not sufficient to reach any conclusion about antidepressant drug effect on suicide.

**Table 2: Risk Differences of the Number of Cases of Suicidal Thoughts or Behaviors in the Pooled Placebo-Controlled Trials of Antidepressants in Pediatric and Adult Patients**

Age Range (years)	Drug-Placebo Difference in Number of Patients of Suicidal Thoughts or Behaviors per 1000 Patients Treated
	Increases Compared to Placebo
<18	14 additional patients
18-24	5 additional patients

- Moderate or severe: Not recommended (2.4)
  - When discontinuing sertraline hydrochloride, reduce dose gradually (2.6, 5.4)
- DOSAGE FORMS AND STRENGTHS---**
- Tablets: 25 mg, 50 mg and 100 mg (3)
- CONTRAINDICATIONS---**
- Concomitant use of monoamine oxidase inhibitors (MAOIs), or use within 14 days of stopping MAOIs (4, 7.1)
  - Concomitant use of pimozide (4, 7.1)
  - Known hypersensitivity to sertraline or excipients (4, 5.4)
- WARNINGS AND PRECAUTIONS---**
- Serotonin Syndrome: Increased risk of co-administered with other serotonergic agents (e.g., SSRI, SNRI, triptans), but also when taken alone. If it occurs, discontinue sertraline hydrochloride and initiate supportive treatment. (5.2)
  - Increased Risk of Bleeding: Concomitant use of aspirin, nonsteroidal anti-inflammatory drugs (NSAIDs), other antiplatelet drugs, warfarin, and other anticoagulants may increase this risk. (5.3)
  - Activation of Mania/Hypomania: Screen patients for bipolar disorder. (5.4)
  - Seizures: Use with caution in patients with seizure disorders. (5.6)
  - Angle Closure Glaucoma: Avoid use of antidepressants, including sertraline hydrochloride, in patients with untreated anatomically narrow angles. (5.7)
  - QTc Prolongation: Sertraline hydrochloride should be used with caution in patients with risk factors for QTc prolongation. (5.10)
  - Sexual Dysfunction: Sertraline hydrochloride may cause symptoms of sexual dysfunction. (5.11)
- ADVERSE REACTIONS---**
- Most common adverse reactions (>5% and twice placebo) in pooled placebo-controlled MDD, OCD, PD, PTSD, SAD and PMDD clinical trials were nausea, diarrhea/loose stool, tremor, dyspepsia, decreased appetite, hyperhidrosis, ejaculation failure, and decreased libido (6.1)
- To report SUSPECTED ADVERSE REACTIONS, contact Camber Pharmaceuticals, Inc., at 1-866-495-8330 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.**

#### ---DRUG INTERACTIONS---

- Protein-bound drugs: Monitor for adverse reactions and reduce dosage of sertraline hydrochloride or other protein-bound drugs (e.g., warfarin) as warranted. (7.1, 12.3)
  - CYP2D6 substrates: Reduce dosage of drugs metabolized by CYP2D6 (7.1, 12.3)
- USE IN SPECIFIC POPULATIONS---**
- Pregnancy: Third trimester use may increase risk for persistent pulmonary hypertension and withdrawal in the neonate (8.1)
  - Pediatric use: Safety and effectiveness of sertraline hydrochloride in pediatric patients other than those with OCD have not been established (8.4)

#### See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

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7.3 False-Positive Screening Tests for Benzodiazepines

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\* Sections or subsections omitted from the full prescribing information are not listed.

	Decreases Compared to Placebo
25-64	1 fewer patient
≥65	6 fewer patients

It is unknown whether the risk of suicidal thoughts and behaviors in pediatric and young adult patients extends to longer-term use, i.e., beyond four months. However, there is substantial evidence from placebo-controlled maintenance trials in adults with MDD that antidepressants delay the recurrence of depression.

Monitor all antidepressant-treated patients for clinical worsening and emergence of suicidal thoughts and behaviors, especially during the initial few months of drug therapy and at times of dosage changes.

Counsel family members or caregivers of patients to monitor for changes in behavior and to alert the healthcare provider. Consider changing the therapeutic regimen, including possibly discontinuing sertraline hydrochloride, in patients whose depression is persistently worse, or who are experiencing emergent suicidal thoughts or behaviors.

###### 5.2 Serotonin Syndrome

Serotonin-norepinephrine reuptake inhibitors (SNRIs) and selective serotonin reuptake inhibitors (SSRIs), including sertraline hydrochloride, 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, 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)]. 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 sertraline hydrochloride with MAOIs is contraindicated. In addition, do not initiate sertraline hydrochloride 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 sertraline hydrochloride, discontinue sertraline hydrochloride before initiating treatment with the MAOI [See Contraindications (4), Drug Interactions (7.1)].

Monitor all patients taking sertraline hydrochloride for the emergence of serotonin syndrome. Discontinue treatment with sertraline hydrochloride and any other concomitant serotonergic agents immediately if the above symptoms occur and institute supportive symptomatic treatment. If concomitant use of sertraline hydrochloride with other serotonergic drugs is clinically warranted, inform patients of the increased risk for serotonin syndrome and monitor for symptoms.

###### 5.3 Increased Risk of Bleeding

Drugs that interfere with serotonin reuptake inhibition, including sertraline hydrochloride, increase the risk of bleeding events. Concomitant use of aspirin, nonsteroidal anti-inflammatory drugs (NSAIDs), other antiplatelet drugs, warfarin, and other anticoagulants 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. Bleeding events related to drugs that interfere with serotonin reuptake have ranged from ecchymosis, hematoma, epistaxis, and petechiae to life-threatening hemorrhages.

Inform patients of the increased risk of bleeding associated with the concomitant use of sertraline hydrochloride and antiplatelet agents or anticoagulants. For patients taking warfarin, carefully monitor the international normalized ratio.

###### 5.4 Activation of Mania or Hypomania

In patients with bipolar disorder, treating a depressive episode with sertraline hydrochloride or another antidepressant may precipitate a manic episode. In controlled clinical trials, patients with bipolar disorder were generally excluded; however, symptoms of mania or hypomania were reported in 0.4% of patients treated with sertraline hydrochloride. Prior to initiating treatment with sertraline hydrochloride, screen patients for any personal or family history of bipolar disorder, mania, or hypomania.

###### 5.5 Discontinuation Syndrome

Adverse reactions after discontinuation of serotonergic antidepressants, particularly after abrupt discontinuation, include: nausea, sweating, dysphoric mood, irritability, agitation, dizziness, sensory disturbances (e.g., paresthesia, such as electric shock sensations), tremor, anxiety, confusion, headache, lethargy, emotional lability, insomnia, hypomania, linitus, and seizures. A gradual reduction in dosage rather than abrupt cessation is recommended whenever possible [See Dosage and Administration (2.6)].

###### 5.6 Seizures

Sertraline hydrochloride has not been systematically evaluated in patients with seizure disorders. Patients with a history of seizures were excluded from clinical studies. Sertraline hydrochloride should be prescribed with caution in patients with a seizure disorder.

###### 5.7 Angle-Closure Glaucoma

The pupillary dilation that occurs following use of many antidepressant drugs including sertraline hydrochloride may trigger an angle closure attack in a patient with anatomically narrow angles who does not have a patent iridectomy. Avoid use of antidepressants, including sertraline hydrochloride, in patients with untreated anatomically narrow angles.

###### 5.8 Hypotension

Hypotension may occur as a result of treatment with SNRIs and SSRIs, including sertraline hydrochloride. Cases with serum sodium lower than 110 mmol/L have been reported. Signs and symptoms of hypotension include headache, difficulty concentrating, memory impairment, confusion, weakness, and unsteadiness, which may lead to falls. Signs and symptoms associated with more severe or acute cases have included hallucination, syncope, seizure, coma, respiratory arrest, and death. In many cases, this hypotension appears to be the result of the syndrome of inappropriate antidiuretic hormone secretion (SIADH).

In patients with symptomatic hyponatremia, discontinue sertraline hydrochloride and institute appropriate medical intervention. Prolonged SSRI use may increase the risk of hyponatremia, and low-volume-depleted may be at greater risk of developing hyponatremia with SSRIs and SNRIs [See Use in Specific Populations (8.5)].

###### 5.9 False-Positive Effects on Screening Tests for Benzodiazepines

False-positive urine immunosay screening tests for benzodiazepines have been reported in patients taking sertraline hydrochloride. This finding is due to lack of specificity of the screening tests. False-positive test results may be expected for several days following discontinuation of sertraline hydrochloride. Confirmatory tests, such as gas chromatography/mass spectrometry, may help distinguish sertraline hydrochloride from benzodiazepines [See Drug Interactions (7.3)].

###### 5.10 QTc Prolongation

During post-marketing use of sertraline, cases of QTc prolongation and Torsade de Pointes (TdP) have been reported. Most reports were confounded by other risk factors. In a randomized, double-blind, placebo- and positive-controlled three-period crossover through QTc study in 54 healthy adult subjects, there was a positive relationship between the length of the rate-adjusted QTc interval and serum sertraline concentration. Therefore, sertraline hydrochloride should be used with caution in patients with risk factors for QTc prolongation [See Drug Interactions (7.1), Clinical Pharmacology (12.2)].

###### 5.11 Sexual Dysfunction

Use of SSRIs, including sertraline hydrochloride, may cause symptoms of sexual dysfunction [See Adverse Reactions (6.1)]. In male patients, SSRI use may cause sexual dysfunction characterized by decreased libido, 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 sertraline hydrochloride and to inquire specifically about changes in sexual function during treatment, because sexual dysfunction 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 therapy.

##### 6 ADVERSE REACTIONS

The following adverse reactions are described in more detail in other sections of the prescribing information:

- Hypersensitivity reactions to sertraline [See Contraindications (4)]
- QTc prolongation and ventricular arrhythmias when taken with pimozide [See Contraindications (4), Clinical Pharmacology (12.2)]
- Suicidal thoughts and behaviors [See Warnings and Precautions (5.1)]
- Serotonin syndrome [See Contraindications (4), Warnings and Precautions (5.2), Drug Interactions (7.1)]
- Increased risk of bleeding [See Warnings and Precautions (5.3)]
- Activation of mania/hypomania [See Warnings and Precautions (5.4)]

- Discontinuation syndrome [See Warnings and Precautions (5.5)]
- Seizures [See Warnings and Precautions (5.6)]
- Angle-closure glaucoma [See Warnings and Precautions (5.7)]
- Hyponatremia [See Warnings and Precautions (5.8)]
- Sexual dysfunction [See Warnings and Precautions (5.11)]

##### 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 varying trials of another drug and may not reflect the rates observed in practice.

The data described below are from randomized, double-blind, placebo-controlled trials of sertraline hydrochloride (mostly 50 mg to 200 mg per day) in 3066 adults diagnosed with MDD, OCD, PD, PTSD, SAD, and PMDD. These 3066 patients exposed to sertraline hydrochloride for 8 to 12 weeks represent 568 patient-years of exposure. The mean age was 40 years; 57% were females and 43% were males.

The most common adverse reactions (>5% and twice placebo) in all pooled placebo-controlled clinical trials of all sertraline hydrochloride-treated patients with MDD, OCD, PD, PTSD, SAD and PMDD were nausea, diarrhea/loose stool, tremor, dyspepsia, decreased appetite, hyperhidrosis, ejaculation failure, and decreased libido (see Table 3). The following are the most common adverse reactions in trials of sertraline hydrochloride (>5% and twice placebo) by indication that were not mentioned previously.

- MDD: somnolence;
- OCD: insomnia, agitation;
- PD: constipation, agitation;
- PTSD: fatigue;
- PMDD: somnolence, dry mouth, dizziness, fatigue, and abdominal pain;
- SAD: insomnia, dizziness, fatigue, dry mouth, malaise.

**Table 3: Common Adverse Reactions in Pooled Placebo-Controlled Trials in Adults with MDD, OCD, PD, PTSD, SAD, and PMDD\***

	Sertraline hydrochloride (N=3066)	Placebo (N=2293)
<b>Cardiac disorders</b>		
Palpitations	4%	2%
<b>Eye disorders</b>		
Visual impairment	4%	2%
<b>Gastrointestinal Disorders</b>		
Nausea	26%	12%
Diarrhea/Loose Stools	20%	10%
Dry mouth	14%	9%
Dyspepsia	8%	4%
Constipation	6%	4%
Vomiting	4%	1%
<b>General disorders and administration site conditions</b>		
Fatigue	12%	8%
<b>Metabolism and nutrition disorders</b>		
Decreased appetite	7%	2%
<b>Nervous system disorders</b>		
Dizziness	12%	8%
Somnolence	11%	6%
Tremor	9%	2%
<b>Psychiatric Disorders</b>		
Insomnia	20%	13%
Agitation	8%	5%
Libido Decreased	6%	2%
<b>Reproductive system and breast disorders</b>		
Ejaculation failure <sup>(†)</sup>	8%	1%
Erectile dysfunction <sup>(†)</sup>	4%	1%
Ejaculation disorder <sup>(†)</sup>	3%	0%
Male sexual dysfunction <sup>(†)</sup>	2%	0%
<b>Skin and subcutaneous tissue disorders</b>		
Hyperhidrosis	7%	3%

\*Denominator used was for male patients only (n=1316 sertraline hydrochloride; n=973 placebo)

<sup>(†)</sup>Adverse reactions that occurred greater than 2% in sertraline hydrochloride-treated patients and at least 2% greater in sertraline hydrochloride-treated patients than placebo-treated patients.

###### Adverse Reactions Leading to Discontinuation in Placebo-Controlled Clinical Trials

In all placebo-controlled studies in patients with MDD, OCD, PD, PTSD, SAD and PMDD, 368 (12%) of the 3066 patients who received sertraline hydrochloride discontinued treatment due to an adverse reaction, compared with 93 (4%) of the 2293 placebo-treated patients. In placebo-controlled studies, the following were the most common adverse reactions leading to discontinuation in sertraline hydrochloride-treated patients:

- MDD, OCD, PD, PTSD, SAD and PMDD: nausea (3%), diarrhea (2%), agitation (2%), and insomnia (2%).
- MDD (>2% and twice placebo): decreased appetite, dizziness, fatigue, headache, somnolence, tremor, and vomiting.
- OCD: somnolence.
- PD: nervousness and somnolence.

###### Male and Female Sexual Dysfunction

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 SSRI treatment. However, reliable estimates of the incidence and severity of untoward experiences involving sexual desire, performance and satisfaction are difficult to obtain, in part because patients and healthcare providers may be reluctant to discuss them. Accordingly, estimates of the incidence of untoward sexual experience and performance cited in labeling may underestimate their actual incidence.

Table 4 below displays the incidence of sexual adverse reactions reported by at least 2% of sertraline hydrochloride-treated patients and twice placebo from pooled placebo-controlled trials. For men and all indications, the most common adverse reactions (>2% and twice placebo) included: ejaculation failure, decreased libido, erectile dysfunction, ejaculation disorder, and male sexual dysfunction. For women, the most common adverse reaction (>2% and twice placebo) was decreased libido.

**Table 4: Most Common Sexual Adverse Reactions (>2% and twice placebo) in Men or Women from sertraline hydrochloride Pooled Controlled Trials in Adults with MDD, OCD, PD, PTSD, SAD, and PMDD**

	Sertraline Hydrochloride (N=1316)	Placebo (N=973)
<b>Men only</b>		
Ejaculation failure	8%	1%
Libido decreased	7%</	



#### 8.4 Pediatric Use

The safety and efficacy of sertraline hydrochloride have been established in the treatment of OCD in pediatric patients aged 6 to 17 [*See Adverse Reactions (6.1)*]. *Clinical Pharmacology (12.3)*, *Clinical Studies (14.2)*. Safety and effectiveness in pediatric patients in patients with OCD below the age of 6 have not been established. Safety and effectiveness have not been established in pediatric patients for indications other than OCD. Two placebo-controlled trials were conducted in pediatric patients with MDD, but the data were not sufficient to support an indication for use in pediatric patients.

#### Monitoring Pediatric Patients Treated with Sertraline Hydrochloride

Monitor all patients being treated with antidepressants for clinical worsening, suicidal thoughts, and unusual changes in behavior, especially during the initial few months of treatment, or at times of dose increases or decreases [*See Boxed Warning, Warnings and Precautions (5.1)*]. Decreased appetite and weight loss have been observed with the use of SSRIs. Monitor weight and growth in pediatric patients treated with an SSRI such as sertraline hydrochloride.

#### Weight Loss in Studies in Pediatric Patients with MDD

In a pooled analysis of two 10-week, double-blind, placebo-controlled, flexible dose (50–200 mg) outpatient trials for MDD (N=573), there was a difference in weight change between sertraline hydrochloride and placebo of roughly 1 kg, for both children (ages 6–11) and adolescents (ages 12–17), in both age groups representing a slight weight loss for the sertraline hydrochloride group compared to a slight gain for the placebo group. For children, about 7% of the sertraline hydrochloride-treated patients had a weight loss greater than 7% of body weight compared to 0% of the placebo-treated patients; for adolescents, about 2% of sertraline hydrochloride-treated patients had a weight loss > 7% of body weight compared to about 1% of placebo-treated patients.

A subset of patients who completed the randomized controlled trials in patients with MDD (sertraline hydrochloride N=99, placebo N=122) were continued into a 24-week, flexible-dose, open-label, extension study. Those subjects who completed 34 weeks of sertraline hydrochloride treatment (10 weeks in a placebo-controlled trial + 24 weeks open-label, n=69) had weight gain that was similar to that expected using data from age-adjusted peers. However, there are no studies that directly evaluate the long-term effects of sertraline hydrochloride on the growth, development, and maturation in pediatric patients.

#### Juvenile Animal Data

A study conducted in juvenile rats at clinically relevant doses showed delay in sexual maturation, but there was no effect on fertility in either males or females.

In this study in which juvenile rats were treated with oral doses of sertraline at 0, 10, 40 or 80 mg/kg/day from postnatal day 21 to 56, a delay in sexual maturation was observed in males treated with 80 mg/kg/day and females treated with doses ≥10 mg/kg/day. There was no effect on male and female reproductive endpoints or neurobehavioral development up to the highest dose tested (80 mg/kg/day), except a decrease in auditory startle response in females at 40 and 80 mg/kg/day at the end of treatment but not at the end of the drug-free period. The highest dose of 80 mg/kg/day produced plasma levels (AUC) of sertraline 5 times those seen in pediatric patients (6–17 years of age) receiving the maximum recommended dose of sertraline (200 mg/day).

#### 8.5 Geriatric Patients

Of the total number of patients in clinical studies of sertraline hydrochloride in patients with MDD, OCD, PD, PTSD, SAD and PMDD, 787 (17%) were ≥ 65 years of age, while 197 (4%) were ≥ 75 years old.

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. In general, dose selection for an elderly patient should be conservative, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

In 354 geriatric subjects treated with sertraline hydrochloride in MDD placebo-controlled trials, the overall profile of adverse reactions was generally similar to that shown in Table 3 [*See Adverse Reactions (6.1)*], except for tremor, arthralgia with an incidence of at least 2% and at a rate greater than placebo in geriatric patients.

SSRIs and SSRIs, including sertraline hydrochloride, 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 (5.8)*].

#### 8.6 Hepatic Impairment

The recommended dosage in patients with mild hepatic impairment (Child-Pugh score 5 or 6) is half the recommended dosage due to increased exposure in this patient population. The use of sertraline hydrochloride in patients with moderate (Child-Pugh score 7 to 10) or severe hepatic impairment (Child-Pugh score 10–15) is not recommended, because sertraline hydrochloride is extensively metabolized, and the effects of sertraline hydrochloride in patients with moderate and severe hepatic impairment have not been studied [*See Dosage and Administration (2.4)*]. *Clinical Pharmacology (12.3)*.

#### 8.7 Renal Impairment

No dose adjustments is needed in patients with mild to severe renal impairment. Sertraline exposure does not appear to be affected by renal impairment [*See Clinical Pharmacology (12.3)*].

#### 9 DRUG ABUSE AND DEPENDENCE

##### 9.1 Controlled Substance

Sertraline hydrochloride contains sertraline, which is not a controlled substance.

##### 9.2 Abuse

In a placebo-controlled, double-blind, randomized study of the comparative abuse liability of sertraline hydrochloride, alprazolam, and d-amphetamine in humans, sertraline hydrochloride did not produce the positive subjective effects indicative of abuse potential, such as euphoria or drug liking, that were observed with the other two drugs.

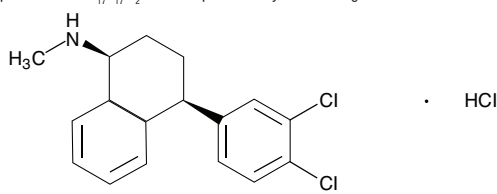
#### 10 OVERDOSAGE

The following have been reported with sertraline 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. 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 proserotonergic drugs may have a higher risk). Gastrointestinal decontamination with activated charcoal should be considered in patients who present early after a sertraline overdose. Consider contacting a Poison Center (1-800-221-2222) or a medical toxicologist for additional overdose management recommendations.

#### 11 DESCRIPTION

Sertraline hydrochloride tablets contains sertraline hydrochloride, an SSRI. Sertraline hydrochloride has a molecular weight of 342.7 and has the following chemical name: (1*S*),4*S*-4-(3,4-dichlorophenyl)-1,2,5,6-tetrahydro-*N*-methyl-1-naphthalenamine hydrochloride. The empirical formula C<sub>17</sub>H<sub>16</sub>Cl<sub>2</sub>NHCl is represented by the following structural formula:



Sertraline hydrochloride is a white or off white crystalline powder that is sparingly soluble in methanol, dimethyl formamide and absolute alcohol; slightly soluble in water, acetone and isopropanol. Sertraline hydrochloride tablets, USP for oral administration contain 28.0 mg, 56.0 mg and 111.9 mg sertraline hydrochloride equivalent to 25, 50, and 100 mg of sertraline and the following inactive ingredients: Microcrystalline cellulose, colloidal silicon dioxide, hydroxypropylcellulose, sodium starch glycolate, magnesium stearate, titanium dioxide, hydroxypropyl methylcellulose, polyethylene glycol and polysorbate 80.

The 25 mg and 50 mg strength also contains FD&C blue no. 2. The 25 mg strength also contains D&C yellow no. 10 aluminum lake. 100 mg strength also contains iron oxide yellow, iron oxide red.

#### 12 CLINICAL PHARMACOLOGY

##### 12.1 Mechanism of Action

Sertraline potentiates serotonergic activity in the central nervous system through inhibition of neuronal reuptake of serotonin (5-HT<sub>2</sub>).

##### 12.2 Pharmacodynamics

Studies at clinically relevant doses have demonstrated that sertraline blocks the uptake of serotonin into human platelets. *In vitro* studies in animals also suggest that sertraline is a potent and selective inhibitor of neuronal serotonin reuptake and has only very weak effects on norepinephrine and dopamine neuronal reuptake. *In vitro* studies have shown that sertraline has a significant affinity for adrenergic (alpha<sub>1</sub>, alpha<sub>2</sub>, beta), cholinergic, GABA, dopaminergic, histaminergic, serotonergic (5HT<sub>1B</sub>, 5HT<sub>2</sub>), or benzodiazepine receptors. The chronic administration of sertraline was found in animals to down regulate brain norepinephrine receptors. Sertraline does not inhibit monoamine oxidase.

##### Alcohol

In healthy subjects, the acute cognitive and psychomotor effects of alcohol were not potentiated by sertraline hydrochloride.

##### Cardiac Electrophysiology

The effect of sertraline on the QTc interval was evaluated in a randomized, double-blind, placebo- and positive-controlled three-period crossover through QTc study in 54 healthy adult subjects. At 2-fold the maximum recommended daily dose (~3-fold the steady-state exposure for sertraline and *N*-desmethylsertraline), the largest mean ΔQTc was 10 ms with upper bound of two-sided 90% confidence interval of 12 ms. The length of the QTc interval was also positively correlated with serum concentrations of sertraline and *N*-desmethylsertraline concentrations. These concentration-based analyses, however, indicated a lesser effect on QTc at maximally observed concentration than in the primary analysis [*See Warnings and Precautions (5)*, *Adverse Reactions (6)*, *Drug Interactions (7)*, *Overdosage (10)*].

#### 12.3 Pharmacokinetics

##### Absorption

Following oral once-daily sertraline hydrochloride dosing over the range of 50 to 200 mg for 14 days, mean peak plasma concentrations (C<sub>max</sub>) of sertraline occurred during 4.5 to 8.4 hours post-dosing. The average terminal elimination half-life of plasma sertraline is about 26 hours. Consistent with the terminal elimination half-life, there is an approximately two-fold accumulation up to steady-state concentrations, which are achieved after one week of once-daily dosing. Linear dose-proportional pharmacokinetics were demonstrated in a single dose study in which the C<sub>max</sub> and area under the plasma concentration time curve (AUC) of sertraline were proportional to dose over a range of 50 to 200 mg. The single dose bioavailability of sertraline hydrochloride tablets is approximately equal to an equivalent dose of sertraline hydrochloride oral solution. Administration with food causes a small increase in C<sub>max</sub> and AUC.

##### Metabolism

Sertraline undergoes extensive first pass metabolism. The principal initial pathway of metabolism for sertraline is *N*-demethylation. *N*-desmethylsertraline has a plasma terminal elimination half-life of 62 to 104 hours. Both *in vitro* biochemical and *in vivo* pharmacological testing have shown *N*-desmethylsertraline to be substantially less active than sertraline. Both sertraline and *N*-desmethylsertraline undergo oxidative deamination and subsequent reduction, hydroxylation, and glucuronide conjugation. In a study of radiolabeled sertraline involving two healthy male subjects, sertraline accounted for less than 5% of the plasma radioactivity. About 40–45% of the administered radioactivity was recovered in urine in 9 days. Unchanged sertraline was not detectable in the urine. For the same period, about 40–45% of the administered radioactivity was accounted for in feces, including 12–14% unchanged sertraline. Desmethylsertraline exhibits time-related, dose dependent increases in AUC (0–24-hour), C<sub>max</sub> and C<sub>min</sub>, with about a 5- to 9-fold decrease in these pharmacokinetic parameters between day 1 and day 14.

##### Protein Binding

*In vitro* protein binding studies performed with radiolabeled 3H-sertraline showed that sertraline is highly bound to serum proteins (98%) in the range of 20 to 500 mg/mL. However, at up to 300 and 200 mg/mL concentrations, respectively, sertraline and *N*-desmethylsertraline did not alter the plasma protein binding of two other highly protein bound drugs, warfarin and propranolol.

##### Studies in Specific Populations

###### Pediatric Patients

Sertraline pharmacokinetics were evaluated in a group of 61 pediatric patients (29 aged 6–12 years, 32 aged 13–17 years) including both males (N=28) and females (N=33). Relative to the adults, pediatric patients aged 6–12 years and 13–17 years showed about 22% lower AUC (0–24 hr) over a range of 50 to 200 mg. The single dose bioavailability of sertraline hydrochloride tablets is similar to that in adults, and no gender-associated differences were observed [*See Dosage and Administration (2.1)*]. *Use in Specific Populations (8.4)*.

###### Geriatric Patients

Sertraline plasma clearance in a group of 16 (8 male, 8 female) elderly patients treated with 100 mg/day of sertraline hydrochloride for 14 days was approximately 40% lower than in a similarly studied group of younger (25 to 52 year old) individuals. Steady-state, therefore, was achieved after 2 to 3 weeks in older patients. There were no significant differences in plasma protein binding observed between the two groups. The effects of sertraline hydrochloride in patients with moderate and severe hepatic impairment have not been studied [*See Dosage and Administration (2.4)*]. *Use in Specific Populations (8.6)*.

###### Renal Impairment

In patients with chronic mild liver impairment (N=10; 8 patients with Child-Pugh scores of 5–6; and 2 patients with Child-Pugh scores of 7–9) who received 50 mg of sertraline hydrochloride per day for 21 days, sertraline clearance was reduced, resulting in approximately 3-fold greater exposure compared to age-matched volunteers with normal hepatic function (N=10). The exposure to desmethylsertraline was approximately 2-fold greater in patients with mild hepatic impairment compared to age-matched volunteers with normal hepatic function. There were no significant differences in plasma protein binding observed between the two groups. The effects of sertraline hydrochloride in patients with moderate and severe hepatic impairment have not been studied [*See Dosage and Administration (2.4)*]. *Use in Specific Populations (8.6)*.

###### Drug Interactions Studies

In a controlled study of a single dose (2 mg) of pimozide, 200 mg sertraline hydrochloride (once daily) co-administration to steady state was associated with a mean increase in pimozide AUC and C<sub>max</sub> of about 40%, but was not associated with any changes in ECG. The highest recommended pimozide dose (10 mg) has not been evaluated in combination with sertraline hydrochloride. The effect on QTc interval and PK parameters at doses higher than 2 mg of pimozide are not known [*See Drug Interactions (7.1)*].

*Drugs Metabolized by CYP2D6*  
Many antidepressant drugs (e.g., SSRIs, including sertraline hydrochloride, and most tricyclic antidepressant drugs) inhibit the biochemical activity of the drug metabolizing isozyme CYP2D6 (debrisoquine hydroxylase), and, thus, may increase the plasma concentrations of drugs that are metabolized by CYP2D6. The drugs for which this potential interaction is of greatest concern are those metabolized primarily by CYP2D6 and that have a narrow therapeutic index (e.g., tricyclic antidepressant drugs and the Type 1C antiarrhythmics propafenone and flecainide). The extent to which this interaction is an important clinical problem depends on the extent of the inhibition of CYP2D6 by the antidepressant and the therapeutic index of the co-administered drug. There is variability among the drugs effective in the treatment of MDD in the extent of clinically important 2D6 inhibition, and in fact sertraline hydrochloride at lower doses has a less prominent inhibitory effect on 2D6 than some others in the class. Nevertheless, even sertraline hydrochloride has the potential for clinically important 2D6 inhibition [*See Drug Interactions (7.1)*].

###### Phenytoin

Clinical trial data suggested that sertraline hydrochloride may increase phenytoin concentrations [*See Drug Interactions (7.1)*].

###### Clonidine

In a study assessing disposition of sertraline hydrochloride (100 mg) and 8 half-life of clonidine administration (800 mg daily), there were increases in sertraline hydrochloride mean AUC (50%), C<sub>min</sub> (24%) and day-time (26%) compared to the placebo group [*See Drug Interactions (7.2)*].

###### Diazepam

In a study comparing the disposition of intravenously administered diazepam before and after 21 days of dosing with either sertraline hydrochloride (50 to 200 mg/day escalating dose) or placebo, there was a 32% decrease relative to baseline in diazepam clearance for the sertraline hydrochloride group compared to a 19% decrease relative to baseline for the placebo group (p<0.03). There was a 23% increase in T<sub>1/2</sub> for desmethylclazepam in the sertraline hydrochloride group compared to a 20% decrease in the placebo group (p<0.03) [*See Drug Interactions (7.2)*].

###### Lithium

In a placebo-controlled trial in normal volunteers, the administration of two doses of sertraline hydrochloride did not significantly alter steady-state lithium levels or the renal clearance of lithium [*See Drug Interactions (7.2)*].

###### Tolbutamide

In a placebo-controlled trial in normal volunteers, administration of sertraline hydrochloride for 22 days (including 200 mg/day for the final 13 days) caused a statistically significant 16% decrease from baseline in the clearance of tolbutamide following an intravenous 1000 mg dose. Sertraline hydrochloride administration did not noticeably change either the plasma protein binding or the apparent volume of distribution of tolbutamide, suggesting that the decreased clearance was due to a change in the metabolism of the drug [*See Drug Interactions (7.2)*].

###### Atenolol

Sertraline hydrochloride (100 mg) when administered to 10 healthy male subjects had no effect on the beta-adrenergic blocking ability of atenolol [*See Drug Interactions (7.2)*].

###### Digoxin

In a placebo-controlled trial in normal volunteers, administration of sertraline hydrochloride for 17 days (including 200 mg/day for the last 10 days) did not change serum digoxin levels or digoxin renal clearance [*See Drug Interactions (7.2)*].

###### Drugs Metabolized by CYP3A4

In three separate *in vivo* interaction studies, sertraline hydrochloride was co-administered with CYP3A4 substrates, terfenadine, carbamazepine, or cispairide under steady-state conditions. The results of these studies indicated that sertraline hydrochloride did not increase plasma concentrations of terfenadine, carbamazepine, or cispairide. These data indicate that sertraline hydrochloride's extent of inhibition of CYP3A4 activity is not likely to be of clinical significance. Results of the interaction study with cispairide indicate that sertraline hydrochloride 200 mg (once daily) induces the metabolism of cispairide (cispairide AUC and C<sub>max</sub> were reduced by about 35%) [*See Drug Interactions (7.2)*].

###### Microsomal Enzyme Induction

Preclinical studies have shown sertraline hydrochloride to induce hepatic microsomal enzymes. In clinical studies, sertraline hydrochloride was shown to induce hepatic enzymes minimally as determined by a small (5%) but statistically significant decrease in antipyrene half-life following administration of 200 mg of sertraline hydrochloride per day for 21 days. This small change in antipyrene half-life reflects a clinically insignificant change in hepatic metabolism.

#### 13 NONCLINICAL TOXICOLOGY

##### 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

###### Carcinogenesis

Lifetime carcinogenicity studies were carried out in CD-1 mice and Long-Evans rats at doses up to 40 mg/kg/day. These doses correspond to 1 times (mice) and 2 times (rats) the maximum recommended human dose (MRHD) of 200 mg/day on a mg/m<sup>2</sup> basis. There was a dose-related increase of liver adenomas in male mice receiving sertraline at 10–40 mg/kg (0.25–1.0 times the MRHD on a mg/m<sup>2</sup> basis). No increase was seen in female mice or in rats of either sex receiving the same treatments, nor was there an increase in hepatocellular carcinomas. Liver adenomas have a variable rate of spontaneous occurrence in the CD-1 mouse and are of unknown significance to humans. There was an increase in follicular adenomas of the thyroid in female rats receiving sertraline at 40 mg/kg (2 times the MRHD on a mg/m<sup>2</sup> basis); this was not accompanied by thyroid hyperplasia. While there was an increase in uterine adenocarcinomas in rats receiving sertraline at 10–40 mg/kg (0.5–2.0 times the MRHD on a mg/m<sup>2</sup> basis) compared to placebo controls, this effect was not clearly drug related.

###### Mutagenesis

Sertraline had no genotoxic effects, with or without metabolic activation, based on the following assays: bacterial mutation assay; mouse lymphoma mutation assay; and tests for cytogenetic aberrations *in vivo* in mouse bone marrow and *in vitro* in human lymphocytes.

###### Impairment of Fertility

A decrease in fertility was seen in one of two rat studies at a dose of 80 mg/kg (3.1 times the maximum recommended human dose on a mg/m<sup>2</sup> basis in adolescents).

#### 14 CLINICAL STUDIES

Efficacy of sertraline hydrochloride was established in the following trials:

- MDD: two short-term trials and one maintenance trials in adults [*See Clinical Studies (14.1)*].
- OCD: three short-term trials in adults and one short-term trial in pediatric patients [*See Clinical Studies (14.2)*].
- PD: three short-term trials and one maintenance trial in adults [*See Clinical Studies (14.3)*].
- PTSD: two short-term trials and one maintenance trial in adults [*See Clinical Studies (14.4)*].
- SAD: two short-term trials and one maintenance trial in adults [*See Clinical Studies (14.5)*].
- PMDD: two short-term trials in adult female patients [*See Clinical Studies (14.6)*].

##### 14.1 Major Depressive Disorder

The efficacy of sertraline hydrochloride as a treatment for MDD was established in two randomized, double-blind, placebo-controlled studies and one double-blind, randomized-withdrawal study following an open label study in adult (ages 18 to 65) outpatients who met the Diagnostic and Statistical Manual of Mental Disorders (DSM-III-R) criteria for MDD (studies MDD-1 and MDD-2).

- Study MDD-1 was an 8-week, 3-arm study with flexible dosing of sertraline hydrochloride, amitriptyline, and placebo. Adult patients received sertraline hydrochloride (N=126, in a daily dose titrated weekly to 50 mg, 100 mg, or 200 mg), amitriptyline (N=123, in a daily dose titrated weekly to 50 mg, 100 mg, or 150 mg), or placebo (N=130).
- Study MDD-2 was a 6-week, multicenter parallel study of three fixed doses of sertraline hydrochloride administered once daily at 50 mg (N=82), 100 mg (N=75), and 200 mg (N=56) doses and placebo (N=76) in the treatment of adult outpatients with MDD.

Overall, these studies demonstrated sertraline hydrochloride to be superior to placebo on the Hamilton Rating Scale for Depression (HAM-D-17) and the Clinical Global Impression Severity (CGI-S) and Severity and Global Improvement (CGI-I) scales. Study MDD-2 was not readily interpretable regarding a dose response relationship for effectiveness.

A third study (Study MDD-3) involved adult outpatients meeting the DSM-III criteria for MDD who had responded by the end of an initial 8-week open treatment phase on sertraline hydrochloride 50–200 mg/day. These patients (n=295) were randomized to continuation on double-blind sertraline hydrochloride 50–200 mg/day or placebo for 44 weeks. A statistically significantly lower relapse rate was observed for patients taking sertraline hydrochloride compared to those on placebo. Sertraline hydrochloride [n=111 (8%)] and placebo [n=31 (39%)]. The mean sertraline hydrochloride dose for completers was 70 mg/day.

Analyses for gender effects and gender effects on outcome did not suggest any differential responsiveness on the basis of sex.

##### 14.2 Obsessive-Compulsive Disorder

###### Adults with OCD

The effectiveness of sertraline hydrochloride in the treatment of OCD was demonstrated in three multicenter placebo-controlled studies of adult (age 18–65) non-depressed outpatients (Studies OCD-1, OCD-2, and OCD-3). Patients in all three studies had moderate to severe OCD (DSM-III-R or DSM-III-R) with mean baseline ratings on the Yale-Brown Obsessive-Compulsive Scale (Y-BOCS) total score ranging from 23 to 25.

- Study OCD-1 was an 8-week randomized, placebo-controlled study with flexible dosing of sertraline hydrochloride in a range of 50 to 200 mg/day, titrated in 50 mg increments every 4 days to a maximally tolerated dose; the mean dose for completers was 186 mg/day. Patients receiving sertraline hydrochloride (N=43) experienced a mean reduction of approximately 4 points on the Y-BOCS total score which was statistically significantly greater than the mean reduction of 2 points in placebo-treated patients (N=44). The mean change in Y-BOCS from baseline to last visit (the primary efficacy endpoint) was -3.79 (sertraline hydrochloride and -1.48 (placebo).
- Study OCD-2 was a 12-week randomized, placebo-controlled fixed-dose study, including sertraline hydrochloride doses of 50, 100, and 200 mg/day. Sertraline hydrochloride (N=240) was titrated to the assigned dose over two weeks in 50 mg increments every 4 days. Patients receiving sertraline hydrochloride doses of 50 and 200 mg/day experienced mean reductions of approximately 6 points on the Y-BOCS total score, which were statistically significantly greater than the approximately 3 point reduction in placebo-treated patients (N=84). The mean change in Y-BOCS from baseline to last visit (the primary efficacy endpoint) was -5.7 (pooled results from sertraline hydrochloride 50 mg, 100 mg, and 150 mg) and -2.85 (placebo).
- Study OCD-3 was a 12-week randomized, placebo controlled study with flexible dosing of sertraline hydrochloride in a range of 50 to 200 mg/day; the mean dose for completers was 185 mg/day. Sertraline hydrochloride (N=241) was titrated to the assigned dose over two weeks in 50 mg increments every 4 days. Patients receiving sertraline hydrochloride experienced a mean reduction of approximately 7 points on the Y-BOCS total score which was statistically significantly greater than the mean reduction of approximately 4 points in placebo-treated patients (N=84). The mean change in Y-BOCS from baseline to last visit (the primary efficacy endpoint) was -6.5 (sertraline hydrochloride and -3.8 (placebo).

Analyses for age and gender effects on outcome did not suggest any differential responsiveness on the basis of age or sex. The effectiveness of sertraline hydrochloride was studied in the risk reduction of OCD relapse. In Study OCD-4, patients ranging in age from 18–79 meeting DSM-III-R criteria for OCD who had responded during a 52-week single-blind trial on sertraline hydrochloride 50–200 mg/day (n=224) were randomized to continuation of sertraline hydrochloride or to substitution of placebo for up to 28 weeks of observation for analysis of discontinuation due to relapse or insufficient clinical response. Response during the double-blind phase was defined as a decrease in the Y-BOCS score of ≥25% compared to baseline and a CGI-I of 1 (very much improved), 2 (much improved) or 3 (minimally improved), insufficient clinical response during the double-blind phase indicated a worsening of the patient's condition that resulted in study discontinuation, as assessed by the investigator. Relapse during the double-blind phase was defined as the following conditions being met (on three consecutive visits for 1, 2, and condition 3 being met at visit 3):

- Condition 2: CGI-I score increased by ≥ 5 points, to a minimum of 20, relative to baseline;
- Condition 3: Worsening of the patient's condition in the investigator's judgment, to justify alternative treatment.

Patients receiving continuation of sertraline hydrochloride treatment experienced a statistically significantly lower rate of discontinuation due to relapse or insufficient clinical response over the subsequent 28 weeks compared to those receiving placebo. This pattern was demonstrated in male and female subjects.

###### Pediatric Patients with OCD

The effectiveness of sertraline hydrochloride for the treatment of OCD was demonstrated in a 12-week, multicenter, placebo-controlled, parallel group study in a pediatric outpatient population (ages 6–17) (Study OCD-5). Sertraline hydrochloride (N=82) was initiated at doses of either 25 mg/day (pediatric patients ages 6–12) or 50 mg/day (adolescents, ages 13–17), and then titrated at 3 and 4 week intervals to a maximum dose of 25% compared to baseline and a CGI-I of 1 (very much improved), 2 (much improved) or 3 (minimally improved), insufficient clinical response during the double-blind phase indicated a worsening of the patient's condition that resulted in study discontinuation, as assessed by the investigator. Relapse during the double-blind phase was defined as the following conditions being met (on three consecutive visits for 1, 2, and condition 3 being met at visit 3):

- Condition 2: CGI-I score increased by ≥ 5 points, to a minimum of 20, relative to baseline;
  - Condition 3: Worsening of the patient's condition in the investigator's judgment, to justify alternative treatment.
- Patients receiving continuation of sertraline hydrochloride treatment experienced a statistically significantly lower rate of discontinuation due to relapse or insufficient clinical response over the subsequent 28 weeks compared to those receiving placebo. This pattern was demonstrated in male and female subjects.
- Pediatric Patients with OCD
- The effectiveness of sertraline hydrochloride for the treatment of OCD was demonstrated in a 12-week, multicenter, placebo-controlled, parallel group study in a pediatric outpatient population (ages 6–17) (Study OCD-5). Sertraline hydrochloride (N=82) was initiated at doses of either 25 mg/day (pediatric patients ages 6–12) or 50 mg/day (adolescents, ages 13–17), and then titrated at 3 and 4 week intervals to a maximum dose of 25% compared to baseline and a CGI-I of 1 (very much improved), 2 (much improved) or 3 (minimally improved), insufficient clinical response during the double-blind phase indicated a worsening of the patient's condition that resulted in study discontinuation, as assessed by the investigator. Relapse during the double-blind phase was defined as the following conditions being met (on three consecutive visits for 1, 2, and condition 3 being met at visit 3):
- Studies PD-1 and PD-2 were 10-week flexible dose studies of sertraline hydrochloride (N=80 Study PD-1 and N=86 Study PD-2) compared to placebo (N=176 Study PD-1 and PD-2). In both studies, sertraline hydrochloride was initiated at 25 mg/day for the first week, then titrated in weekly increments of 50 mg per day to a maximum dose of 200 mg/day on the basis of clinical response and toleration. The mean sertraline hydrochloride doses for completers to 10 weeks were 131 mg/day and 144 mg/day, respectively, for Studies PD-1 and PD-2. In these studies, sertraline hydrochloride was shown to be statistically significantly more effective than placebo on change from baseline in panic attack frequency and on the Clinical Global Impression Severity (CGI-S) of illness and Global Improvement (CGI-I) scores. The difference between sertraline hydrochloride and placebo in reduction from baseline in the number of full panic attacks was approximately 2 panic attacks per week in both studies.
  - Study PD-3 was a 12-week randomized, double-blind fixed-dose study, including sertraline hydrochloride doses of 50, 100, and 200 mg/day. Patients receiving sertraline hydrochloride (50 mg N=43, 100 mg N=44, 200 mg N=45) experienced a statistically significantly greater reduction in panic attack frequency than patients receiving placebo (N=45). Study PD-3 was not readily interpretable regarding a dose response relationship for effectiveness.

Subgroup analyses did not indicate that there were any differences in treatment outcomes as a function of age, race, or gender. In Study PD-4, patients meeting DSM-III-R criteria for PD who had responded during a 52-week open trial on sertraline hydrochloride 50–200 mg/day (N=183) were randomized to continuation of sertraline hydrochloride or to substitution of placebo for up to 28 weeks of observation for discontinuation due to relapse or insufficient clinical response. Response during the

open phase was defined as a CGI-S score of 1 (very much improved) or 2 (much improved). Insufficient clinical response in the double-blind phase indicated a worsening of the patient's condition that resulted in study discontinuation, as assessed by the investigator. Relapse during the double-blind phase was defined as the following conditions being met on three consecutive visits:

- (1) CGI-I ≥ 3;
- (2) meets DSM-III-R criteria for PD;
- (3) number of panic attacks greater than at baseline.

Patients receiving continued sertraline hydrochloride treatment experienced a statistically significantly lower rate of discontinuation due to relapse or insufficient clinical response over the subsequent 28 weeks compared to those receiving placebo. This pattern was demonstrated in male and female subjects.

#### 14.4 Posttraumatic Stress Disorder

The effectiveness of sertraline hydrochloride in the treatment of PTSD was established in two multicenter placebo-controlled studies (Studies PSTD-1 and PSTD-2) of adult outpatients who met DSM-III-R criteria for PTSD. The mean duration of PTSD for these patients was 12 years (Studies PSTD-1 and PSTD-2 combined) and 44% of