

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

SERTRALINE HYDROCHLORIDE capsules, for oral use

Initial U.S. Approval: 1991

WARNING: SUICIDAL THOUGHTS AND BEHAVIORS

See full prescribing information for complete boxed warning.

Increased risk of suicidal thoughts and behavior in pediatric and young adult patients taking antidepressants. Closely monitor all antidepressant-treated patients for clinical worsening and emergence of suicidal thoughts and behaviors (5.1)

RECENT MAJOR CHANGES

Warnings and Precautions (5.2, 5.3)

8/2023

INDICATIONS AND USAGE

Sertraline Hydrochloride (HCl) Capsules is a selective serotonin reuptake inhibitor (SSRI) indicated for the treatment of (1):

- Major depressive disorder (MDD) in adults
- Obsessive-compulsive disorder (OCD) in adults and pediatric patients 6 years and older

DOSAGE AND ADMINISTRATION

- Do not initiate treatment with Sertraline HCl Capsules. Use another sertraline HCl product for initial dosage, titration, and dosages below 150 mg once daily (2.1)
- Recommended dosage is 150 mg or 200 mg once daily (2.1)
- Maximum recommended dosage is 200 mg once daily (2.1)
- Swallow capsules whole. Do not open, crush, or chew (2.2)
- When discontinuing Sertraline HCl Capsules, reduce dose gradually whenever possible. Gradual dosage reduction will require use of another sertraline HCl product (2.5, 5.5)

DOSAGE FORMS AND STRENGTHS

- Capsules: 150 mg and 200 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)

WARNINGS AND PRECAUTIONS

- Serotonin Syndrome: Increased risk when co-administered with other serotonergic agents, but also when taken alone. If it occurs, discontinue Sertraline HCl Capsules and serotonergic agents and initiate supportive

treatment (4, 5.2, 7.1)

- 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 or Hypomania: Screen patients for bipolar disorder (5.4)
- Discontinuation Syndrome: When discontinuing Sertraline HCl Capsules, reduce dosage gradually whenever possible, and monitor for discontinuation symptoms. Gradual reduction will require use of another sertraline HCl product (5.5)
- Seizures: Use with caution in patients with seizure disorders (5.6)
- Angle Closure Glaucoma: Avoid use of antidepressants, including Sertraline HCl Capsules, in patients with untreated anatomically narrow angles (5.7)
- QTc Prolongation: Sertraline HCl Capsules should be used with caution in patients with risk factors for QTc prolongation (5.10)
- Allergic Reactions to FD&C Yellow No. 5 (Tartrazine): Contains FD&C Yellow No. 5 (tartrazine) which may cause allergic-type reactions (including bronchial asthma) in certain susceptible persons (5.11)
- Sexual Dysfunction: Sertraline HCl Capsules may cause symptoms of sexual dysfunction (5.12)

ADVERSE REACTIONS

Most common adverse reactions ($\geq 5\%$ and twice placebo) in pooled placebo-controlled clinical trials with sertraline HCl were nausea, diarrhea/loose stool, tremor, dyspepsia, decreased appetite, hyperhidrosis, ejaculation failure, and decreased libido (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Almatica Pharma LLC at 1-877-447-7979 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 HCl Capsules 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 symptoms of poor adaptation (respiratory distress, temperature instability, feeding difficulty, hypotonia, irritability) in the neonate (8.1)
- Pediatric use: Safety and effectiveness in pediatric patients other than those with OCD (6 to 17 years) have not been established (8.4)
- Hepatic Impairment: Not recommended (8.6)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 8/2023

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FULL PRESCRIBING INFORMATION

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 (HCl) Capsules is indicated for the treatment of the following [see *Clinical Studies (14)*]:

- Major depressive disorder (MDD) in adults
- Obsessive-compulsive disorder (OCD) in adults and pediatric patients 6 years and older

2 DOSAGE AND ADMINISTRATION

2.1 Dosage in Patients with MDD and OCD

Do not initiate treatment with Sertraline HCl Capsules because the only available dose strengths are 150 mg and 200 mg. Use another sertraline HCl product for initial dosage, titration, and dosages below 150 mg once daily. Refer to Prescribing Information of the other sertraline HCl products for the recommended dosage for those products.

Sertraline HCl Capsules can be initiated in patients receiving 100 mg or 125 mg of sertraline HCl for at least one week. The recommended dosage of Sertraline HCl Capsules is 150 mg or 200 mg once daily. The maximum recommended dosage is 200 mg once daily.

2.2 Administration Instructions

Administer Sertraline HCl Capsules orally. Swallow capsules whole; do not open, crush, or chew.

2.3 Screen for Bipolar Disorder Prior to Starting Sertraline HCl Capsules

Prior to initiating treatment with Sertraline HCl Capsules 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 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 HCl Capsules. In addition, at least 14 days must elapse after stopping Sertraline HCl Capsules before starting an MAOI antidepressant [see *Contraindications (4)*, *Warnings and Precautions (5.2)*].

2.5 Discontinuation of Treatment with Sertraline HCl Capsules

Adverse reactions may occur upon discontinuation of Sertraline HCl Capsules [see *Warnings and Precautions (5.5)*]. Gradually reduce the dosage rather than stopping Sertraline HCl Capsules abruptly whenever possible. Given that dosage strengths lower than 150 mg of Sertraline HCl Capsules are not available, gradual dosage reduction will require the use of another sertraline HCl product.

3 DOSAGE FORMS AND STRENGTHS

150 mg capsules: Hard shell capsules, with "ALM" printed axially on the opaque yellow cap and "664" printed axially on the opaque white body.

200 mg capsules: Hard shell capsules, with "ALM" printed axially on the opaque yellowish green cap and "672" printed axially on the opaque white body.

Dosage strengths are based on the active moiety, sertraline. The 150 mg capsules contain 168 mg of sertraline HCl. The 200 mg capsules contain 224 mg of sertraline HCl.

4 CONTRAINDICATIONS

Sertraline HCl Capsules are 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 or the excipients in Sertraline HCl Capsules (e.g., anaphylaxis, angioedema) [see *Adverse Reactions* (6.1, 6.2)].

5 WARNINGS AND PRECAUTIONS

5.1 Suicidal Thoughts and Behaviors in Adolescent and Young Adults

In pooled analyses of placebo-controlled trials of antidepressant drugs (SSRIs and other antidepressant classes) that included approximately 77,000 adult patients and over 4,500 pediatric patients, the incidence of suicidal thoughts and behaviors in antidepressant-treated patients age 24 years and younger was greater than in placebo-treated patients. There was considerable variation in risk of suicidal thoughts and behaviors among drugs, but there was an increased risk identified in young patients for most drugs studied. There were differences in absolute risk of suicidal thoughts and behaviors across the different indications, with the highest incidence in patients with MDD. The drug-placebo differences in the number of cases of suicidal thoughts and behaviors per 1,000 patients treated are provided in Table 1.

Table 1: Risk Differences of the Number of Patients of Suicidal Thoughts or Behavior in the Pooled Placebo-Controlled Trials of Antidepressants in Pediatric and Adult Patients

Age Range	Drug-Placebo Difference in Number of Patients of Suicidal Thoughts or Behaviors per 1,000 Patients Treated
	Increases Compared to Placebo
<18 years old	14 additional patients
18 to 24 years old	5 additional patients
	Decreases Compared to Placebo
25 to 64 years old	1 fewer patient
≥65 years old	6 fewer patients

It is unknown whether the risk of suicidal thoughts and behaviors in children, adolescents, and young adults

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 and that depression itself is a risk factor for suicidal thoughts and behaviors.

Monitor all antidepressant-treated patients for any indication 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 HCl Capsules, in patients whose depression is persistently worse, or who are experiencing emergent suicidal thoughts or behaviors.

5.2 Serotonin Syndrome

SSRIs, including Sertraline HCl Capsules, 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)*]. 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 HCl Capsules with MAOIs is contraindicated. In addition, do not initiate Sertraline HCl Capsules 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 ingestion 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 HCl Capsules, discontinue Sertraline HCl Capsules before initiating treatment with the MAOI [see *Contraindications (4)*, *Drug Interactions (7.1)*].

Monitor all patients taking Sertraline HCl Capsules for the emergence of serotonin syndrome. Discontinue treatment with Sertraline HCl Capsules and any concomitant serotonergic agents immediately if the above symptoms occur, and initiate supportive symptomatic treatment. If concomitant use of Sertraline HCl Capsules 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 HCl Capsules, 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. 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 events related to drugs that interfere with serotonin reuptake have ranged from ecchymosis, hematoma, epistaxis, and petechiae to life-threatening hemorrhages.

Inform patients about the increased risk of bleeding associated with the concomitant use of Sertraline HCl Capsules 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 HCl Capsules or another antidepressant may precipitate a mixed/manic episode. In controlled clinical trials with another sertraline HCl product, patients with bipolar disorder were generally excluded; however, symptoms of mania or hypomania were reported in 0.4% of patients treated with sertraline. Prior to initiating treatment with Sertraline HCl Capsules, screen patients for any personal or family history of bipolar disorder, mania, or hypomania [see *Dosage and Administration* (2.3)].

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, tinnitus, and seizures. A gradual reduction in dosage rather than abrupt cessation is recommended whenever possible [see *Dosage and Administration* (2.5)].

5.6 Seizures

Sertraline HCl has not been systematically evaluated in patients with seizure disorders. Patients with a history of seizures were excluded from clinical studies. Sertraline HCl Capsules 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 HCl, 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 HCl Capsules, in patients with untreated anatomically narrow angles.

5.8 Hyponatremia

Hyponatremia may occur as a result of treatment with SSRIs, including Sertraline HCl Capsules. Cases with serum sodium lower than 110 mmol/L have been reported with another sertraline HCl product. Signs and symptoms of hyponatremia 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 hyponatremia appears to be the result of the syndrome of inappropriate antidiuretic hormone secretion (SIADH).

In patients with symptomatic hyponatremia, discontinue Sertraline HCl Capsules and institute appropriate medical intervention. Elderly patients, patients taking diuretics, and those who are volume-depleted may be at greater risk of developing hyponatremia with SSRIs [see *Use in Specific Populations* (8.5)].

5.9 False-Positive Effects on Screening Tests for Benzodiazepines

False-positive urine immunoassay screening tests for benzodiazepines have been reported in patients taking another sertraline HCl product. 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 HCl Capsules. Confirmatory tests, such as gas chromatography/mass spectrometry, will help distinguish Sertraline HCl Capsules 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 thorough 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 HCl Capsules should be used with caution in patients with risk factors for QTc prolongation [see *Drug Interactions* (7.1), *Clinical Pharmacology* (12.2)].

5.11 Allergic Reactions to FD&C Yellow No. 5 (Tartrazine)

Sertraline HCl Capsules contain FD&C Yellow No. 5 (tartrazine), which may cause allergic-type reactions (including bronchial asthma) in certain susceptible persons. Although the overall incidence of FD&C Yellow No. 5 (tartrazine) sensitivity in the general population is low, it is frequently seen in patients who also have aspirin hypersensitivity.

5.12 Sexual Dysfunction

Use of SSRIs, including Sertraline HCl Capsules, 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 Sertraline HCl Capsules 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 described in more detail in other sections of the prescribing information:

- Hypersensitivity reactions to sertraline or excipients of Sertraline HCl Capsules [see *Contraindications* (4)]
- Suicidal Thoughts and Behaviors in Adolescent and Young Adults [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 or 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)]
- QTc Prolongation [see *Warnings and Precautions* (5.10)]
- Allergic reactions to FD&C Yellow No. 5 (Tartrazine) [see *Warnings and Precautions* (5.11)]
- Sexual Dysfunction [see *Warnings and Precautions* (5.12)]

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 the rates observed in practice.

The safety of Sertraline HCl Capsules for the treatment of MDD and OCD is based on adequate and well-controlled studies of another sertraline HCl product. Below is a display of adverse reactions of sertraline HCl (referred to as “sertraline” in this section) from those adequate and well-controlled studies in MDD, OCD, and other conditions.

The data described below reflect exposure in randomized, double-blind, placebo-controlled trials of sertraline in 3066 adults. These 3066 patients exposed to sertraline 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 ($\geq 5\%$ and twice placebo) in all pooled placebo-controlled clinical trials of all sertraline-treated patients (MDD, OCD, and other conditions) were nausea, diarrhea/loose stool, tremor, dyspepsia, decreased appetite, hyperhidrosis, ejaculation failure, and decreased libido (see Table 2). The following are the most common adverse reactions in trials of sertraline ($\geq 5\%$ and twice placebo) by indication that were not mentioned previously.

- MDD: somnolence
- OCD: insomnia, agitation

Table 2: Common Adverse Reactions (Greater than 2% of Adults with MDD, OCD, and Other Conditions Treated with Sertraline Hydrochloride and Greater than or Equal to Twice the Incidence of Placebo) in Pooled Placebo-Controlled Trials*

	Sertraline Hydrochloride (N=3066) %	Placebo (N=2293) %
Cardiac disorders		
Palpitations	4	2
Eye disorders		
Visual impairment	4	2
Gastrointestinal Disorders		
Nausea	26	12
Diarrhea/Loose Stools	20	10
Dry mouth	14	9
Dyspepsia	8	4
Constipation	6	4
Vomiting	4	1
General disorders and administration site conditions		
Fatigue	12	8
Metabolism and nutrition disorders		
Decreased appetite	7	2
Nervous system disorders		
Dizziness	12	8
Somnolence	11	6
Tremor	9	2

Psychiatric Disorders		
Insomnia	20	13
Agitation	8	5
Libido Decreased	6	2
Reproductive system and breast disorders		
Ejaculation failure ⁽¹⁾	8	1
Erectile dysfunction ⁽¹⁾	4	1
Ejaculation disorder ⁽¹⁾	3	0
Male sexual dysfunction ⁽¹⁾	2	0
Skin and subcutaneous tissue disorders		
Hyperhidrosis	7	3

⁽¹⁾ Denominator used was for male patients only (n=1316 sertraline; n=973 placebo).

* 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, 368 (12%) of the 3066 patients who received sertraline 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 common adverse reactions leading to discontinuation in sertraline-treated patients:

- All sertraline -treated patients (MDD, OCD, and Other Conditions): 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.

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 3 below displays the incidence of sexual adverse reactions reported by at least 2% of sertraline -treated patients and twice placebo from pooled placebo-controlled trials of MDD, OCD, and other conditions. 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 ($\geq$ 2% and twice placebo) was decreased libido.

Table 3: Most Common Sexual Adverse Reactions ($\geq 2\%$ and twice placebo) in Men or Women from Sertraline Hydrochloride Pooled Controlled Trials in Adults with MDD, OCD, and Other Conditions

	Sertraline Hydrochloride %	Placebo %
Men only	(N=1316)	(N=973)
Ejaculation failure	8	1
Libido decreased	7	2
Erectile dysfunction	4	1
Ejaculation disorder	3	0
Male sexual dysfunction	2	0
Women only	(N=1750)	(N=1320)
Libido decreased	4	2

Adverse Reactions in Pediatric Patients

In 281 pediatric patients treated with sertraline in placebo-controlled studies, the overall profile of adverse reactions was generally similar to that seen in adult studies. Adverse reactions that do not appear in Table 2 (most common adverse reactions in adults) yet were reported in at least 2% of pediatric patients and at a rate of at least twice the placebo rate include fever, hyperkinesia, urinary incontinence, aggression, epistaxis, purpura, arthralgia, decreased weight, muscle twitching, and anxiety.

Other Adverse Reactions Observed During the Premarketing Evaluation of Sertraline

Other infrequent adverse reactions, not described elsewhere in the prescribing information, occurring at an incidence of $< 2\%$ in patients treated with sertraline were:

Cardiac disorders – tachycardia

Ear and labyrinth disorders – tinnitus

Endocrine disorders - hypothyroidism

Eye disorders - mydriasis, blurred vision

Gastrointestinal disorders - hematochezia, melena, rectal hemorrhage

General disorders and administration site conditions - edema, gait disturbance, irritability, pyrexia

Hepatobiliary disorders - elevated liver enzymes

Immune system disorders - anaphylaxis

Metabolism and nutrition disorders - diabetes mellitus, hypercholesterolemia, hypoglycemia, increased appetite

Musculoskeletal and connective tissue disorders – arthralgia, muscle spasms, tightness, or twitching

Nervous system disorders - ataxia, coma, convulsion, decreased alertness, hypoesthesia, lethargy, psychomotor hyperactivity, syncope

Psychiatric disorders - aggression, bruxism, confusional state, euphoric mood, hallucination

Renal and urinary disorders - hematuria

Reproductive system and breast disorders - galactorrhea, priapism, vaginal hemorrhage

Respiratory, thoracic and mediastinal disorders - bronchospasm, epistaxis, yawning

Skin and subcutaneous tissue disorders - alopecia; cold sweat; dermatitis; dermatitis bullous; pruritus; purpura; erythematous, follicular, or maculopapular rash; urticaria

Vascular disorders - hemorrhage, hypertension, vasodilation

6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of another sertraline product. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Bleeding or clotting disorders - increased coagulation times (altered platelet function)

Cardiac disorders - AV block, bradycardia, atrial arrhythmias, QTc-interval prolongation, ventricular tachycardia (including Torsade de Pointes) [see *Clinical Pharmacology* (12.2)]

Endocrine disorders - gynecomastia, hyperprolactinemia, menstrual irregularities, SIADH

Eye disorders - blindness, optic neuritis, cataract

Hepatobiliary disorders - severe liver events (including hepatitis, jaundice, liver failure with some fatal outcomes), pancreatitis

Hemic and lymphatic disorders - agranulocytosis, aplastic anemia and pancytopenia, leukopenia, thrombocytopenia, lupus-like syndrome, serum sickness

Immune system disorders - angioedema

Metabolism and nutrition disorders - hyponatremia, hyperglycemia

Musculoskeletal and connective tissue disorders - rhabdomyolysis, trismus

Nervous system disorders - serotonin syndrome, extrapyramidal symptoms (including akathisia and dystonia), oculogyric crisis

Psychiatric disorders - psychosis, enuresis, paroniria

Renal and urinary disorders - acute renal failure

Respiratory, thoracic and mediastinal disorders - pulmonary hypertension, anosmia, hyposmia

Skin and subcutaneous tissue disorders - photosensitivity skin reaction and other severe cutaneous reactions, which potentially can be fatal, such as Stevens-Johnson Syndrome (SJS) and toxic epidermal necrolysis (TEN)

Vascular disorders - cerebrovascular spasm (including reversible cerebral vasoconstriction syndrome and Call-Fleming syndrome), vasculitis

7 DRUG INTERACTIONS

7.1 Clinically Significant Drug Interactions

Table 4 includes clinically significant drug interactions with Sertraline HCl Capsules [see *Clinical Pharmacology* (12.3)].

Table 4. Clinically-Significant Drug Interactions with Sertraline HCl Capsules

Monoamine Oxidase Inhibitors (MAOIs)	
<i>Clinical Impact:</i>	The concomitant use of SSRIs, including Sertraline HCl Capsules, and MAOIs increases the risk of serotonin syndrome.
<i>Intervention:</i>	Sertraline HCl Capsules is contraindicated in patients taking MAOIs, including MAOIs such as linezolid or intravenous methylene blue [see <i>Dosage and Administration (2.4), Contraindications (4), Warnings and Precautions (5.2)</i>].
Pimozide	
<i>Clinical Impact:</i>	Increased plasma concentrations of pimozide, a drug with a narrow therapeutic index, may increase the risk of QTc prolongation and ventricular arrhythmias.
<i>Intervention:</i>	Concomitant use of pimozide and Sertraline HCl Capsules is contraindicated [see <i>Contraindications (4)</i>].
Other Serotonergic Drugs	
<i>Clinical Impact:</i>	Concomitant use of Sertraline HCl Capsules with other serotonergic drugs (including other SSRIs, SNRIs, triptans, tricyclic antidepressants, opioids, lithium, buspirone, amphetamines, tryptophan, and St. John's Wort) increases the risk of serotonin syndrome.
<i>Intervention:</i>	Monitor patients for signs and symptoms of serotonin syndrome, particularly during treatment initiation and dosage increases. If serotonin syndrome occurs, consider discontinuation of Sertraline HCl Capsules and/or concomitant serotonergic drugs [see <i>Warnings and Precautions (5.2)</i>].
Drugs that Interfere with Hemostasis (antiplatelet agents and anticoagulants)	
<i>Clinical Impact:</i>	The concurrent use of an antiplatelet agent or anticoagulant with Sertraline HCl Capsules may potentiate the risk of bleeding.
<i>Intervention:</i>	Inform patients of the increased risk of bleeding associated with the concomitant use of Sertraline HCl Capsules and antiplatelet agents and anticoagulants. For patients taking warfarin, carefully monitor the international normalized ratio [see <i>Warnings and Precautions (5.3)</i>].
Drugs Highly Bound to Plasma Protein	
<i>Clinical Impact:</i>	Sertraline is highly bound to plasma protein. The concomitant use of Sertraline HCl Capsules with another drug that is highly bound to plasma protein may increase free concentrations of sertraline or other tightly-bound drugs in plasma [see <i>Clinical Pharmacology (12.3)</i>].
<i>Intervention:</i>	Monitor for adverse reactions and reduce dosage of Sertraline HCl Capsules or other protein-bound drugs as warranted.
Drugs Metabolized by CYP2D6	
<i>Clinical Impact:</i>	Sertraline HCl Capsules are a CYP2D6 inhibitor [see <i>Clinical Pharmacology (12.3)</i>]. The concomitant use of Sertraline HCl capsules with a CYP2D6 substrate may increase the exposure of the CYP2D6 substrate.
<i>Intervention:</i>	Decrease the dosage of a CYP2D6 substrate if needed with concomitant Sertraline HCl Capsules use. Conversely, an increase in dosage of a CYP2D6 substrate may

	be needed if Sertraline HCl Capsules are discontinued.
Phenytoin	
<i>Clinical Impact:</i>	Phenytoin is a narrow therapeutic index drug. Sertraline HCl Capsules may increase phenytoin concentrations.
<i>Intervention:</i>	Monitor phenytoin levels when initiating or titrating Sertraline HCl Capsules. Reduce phenytoin dosage if needed.
Drugs that Prolong the QTc Interval	
<i>Clinical Impact:</i>	The risk of QTc prolongation and/or ventricular arrhythmias (e.g., TdP) is increased with concomitant use of Sertraline HCl Capsules with other drugs which prolong the QTc interval [see <i>Warnings and Precautions (5.10)</i> , <i>Clinical Pharmacology (12.2)</i>].
<i>Intervention:</i>	Pimozide is contraindicated for use with Sertraline HCl Capsules. Avoid the concomitant use of drugs known to prolong the QTc interval.

7.2 Drugs Having No Clinically Important Interactions with Sertraline HCl

Based on pharmacokinetic studies with another sertraline HCl formulation, no dosage adjustment of Sertraline HCl Capsules is necessary when used in combination with cimetidine. Additionally, no dosage adjustment is required for diazepam, lithium, atenolol, tolbutamide, digoxin, and drugs metabolized by CYP3A4, when Sertraline HCl Capsules is administered concomitantly [see *Clinical Pharmacology (12.3)*].

7.3 False-Positive Screening Tests for Benzodiazepines

False-positive urine immunoassay screening tests for benzodiazepines have been reported in patients taking another sertraline HCl product. 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 HCl Capsules. Confirmatory tests, such as gas chromatography/mass spectrometry, will distinguish sertraline from benzodiazepines.

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 should encourage patients to enroll 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 (5.3)* and *Clinical Considerations*].

Overall, available published epidemiologic studies of pregnant women exposed to sertraline in the first trimester suggest no difference in major birth defect risk compared to the background rate for major birth defects in comparator populations. Some studies have reported increases for specific major birth defects; however, these study results are inconclusive (see *Data*). There are clinical considerations regarding neonates exposed to SSRIs, including Sertraline HCl Capsules, during the third trimester of pregnancy (see

Clinical Considerations).

Although no malformations were observed in animal reproduction studies, delayed fetal ossification was observed when sertraline was administered during the period of organogenesis at doses less than the maximum recommended human dose (MRHD) in rats and doses approximately 4 times the MRHD in rabbits on a mg/m² basis in adults. When sertraline was administered to female rats during the last third of gestation, there was an increase in the number of stillborn pups and pup deaths during the first four days after birth at the MRHD (*see Data*).

The background risk of major birth defects and miscarriage for the indicated population are unknown. In the U.S. 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. Advise a pregnant woman of possible risks to the fetus when prescribing Sertraline HCl Capsules.

Clinical Considerations

Disease-Associated Maternal and/or Embryo/Fetal Risk

A prospective longitudinal study followed 201 pregnant women with a history of major depression who were euthymic taking antidepressants at the beginning of pregnancy. The women who discontinued antidepressants during pregnancy were more likely to experience a relapse of major depression than women who continued antidepressants. Consider the risks of untreated depression when discontinuing or changing treatment with antidepressant medication during pregnancy and postpartum.

Maternal Adverse Reactions

Use of Sertraline HCl Capsules in the month before delivery may be associated with an increased risk of postpartum hemorrhage [*see Warnings and Precautions (5.3)*].

Fetal/Neonatal Adverse Reactions

Exposure to SSRIs, including Sertraline HCl Capsules, in late pregnancy may lead to an increased risk for neonatal complications requiring prolonged hospitalization, respiratory support, and tube feeding, and/or persistent pulmonary hypertension of the newborn (PPHN).

When treating a pregnant woman with Sertraline HCl Capsules during the third trimester, carefully consider both the potential risks and benefits of treatment. Monitor neonates who were exposed to sertraline in the third trimester of pregnancy for PPHN and drug discontinuation syndrome (*see Data*).

Data

Human Data

Third Trimester Exposure

Neonates exposed to sertraline and other SSRIs late in the third trimester have developed complications requiring prolonged hospitalization, respiratory support, and tube feeding. These findings are based on post-marketing reports. Such complications can arise immediately upon delivery. Reported clinical findings have included respiratory distress, cyanosis, apnea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycemia, hypotonia, hypertonia, hyperreflexia, tremor, jitteriness, irritability, and constant crying. These features are consistent with either a direct toxic effect of SSRIs or, possibly, a drug discontinuation syndrome. In some cases, the clinical picture was consistent with serotonin syndrome [*see Warnings and Precautions (5.2)*].

Exposure during late pregnancy to SSRIs may have an increased risk for persistent pulmonary hypertension of the newborn (PPHN). PPHN occurs in 1 to 2 per 1,000 live births in the general population and is associated with substantial neonatal morbidity and mortality. In a retrospective case-control study of 377

women whose infants were born with PPHN and 836 women whose infants were born healthy, the risk for developing PPHN was approximately six-fold higher for infants exposed to SSRIs after the 20th week of gestation compared to infants who had not been exposed to antidepressants during pregnancy. A study of 831,324 infants born in Sweden in 1997 to 2005 found a PPHN risk ratio of 2.4 (95% CI 1.2 to 4.3) associated with patient-reported maternal use of SSRIs “in early pregnancy” and a PPHN risk ratio of 3.6 (95% CI 1.2 to 8.3) associated with a combination of patient-reported maternal use of SSRIs “in early pregnancy” and an antenatal SSRI prescription “in later pregnancy”.

First Trimester Exposure

The weight of evidence from epidemiologic studies of pregnant women exposed to sertraline in the first trimester suggest no difference in major birth defect risk compared to the background rate for major birth defects in pregnant women who were not exposed to sertraline. A meta-analysis of studies suggest no increase in the risk of total malformations (summary odds ratio=1.01, 95% CI=0.88 to 1.17) or cardiac malformations (summary odds ratio=0.93, 95% CI=0.70 to 1.23) among offspring of women with first trimester exposure to sertraline. An increased risk of congenital cardiac defects, specifically septal defects, the most common type of congenital heart defect, was observed in some published epidemiologic studies with first trimester sertraline exposure; however, most of these studies were limited by the use of comparison populations that did not allow for the control of confounders such as the underlying depression and associated conditions and behaviors, which may be factors associated with increased risk of these malformations.

Animal Data

Reproduction studies have been performed in rats and rabbits at doses up to 80 mg/kg/day and 40 mg/kg/day, respectively. These doses correspond to approximately 4 times the maximum recommended human dose (MRHD) of 200 mg/day on a mg/m² basis in adults. There was no evidence of malformation at any dose level. When pregnant rats and rabbits were given sertraline during the period of organogenesis, delayed ossification was observed in fetuses at doses of 10 mg/kg (0.5 times the MRHD on a mg/m² basis) in rats and 40 mg/kg (3.9 times the MRHD on a mg/m² basis) in rabbits. When female rats received sertraline during the last third of gestation and throughout lactation, there was an increase in stillborn pups and pup deaths during the first 4 days after birth. Pup body weights were also decreased during the first four days after birth. These effects occurred at a dose of 20 mg/kg (1 times the MRHD on a mg/m² basis). The no effect dose for rat pup mortality was 10 mg/kg (0.5 times the MRHD on a mg/m² basis). The decrease in pup survival was shown to be due to *in utero* exposure to sertraline. The clinical significance of these effects is unknown.

8.2 Lactation

Risk Summary

Available data from published literature demonstrate low levels of sertraline and its metabolites in human milk (*see Data*). There are no data on the effects of sertraline on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother’s clinical need for Sertraline HCl Capsules and any potential adverse effects on the breastfed infant from the drug or from the underlying maternal condition.

Data

In a published pooled analysis of 53 mother-infant pairs, exclusively human milk-fed infants had an average of 2% (range 0% to 15%) of the sertraline serum levels measured in their mothers. No adverse reactions were observed in these infants.

8.4 Pediatric Use

The safety and effectiveness of Sertraline HCl Capsules 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 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 with another sertraline HCl product 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 HCl Capsules

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 SSRIs including Sertraline HCl Capsules.

Weight Loss in Studies in Pediatric Patients with MDD

In a pooled analysis of two 10-week, double-blind, placebo-controlled, flexible dose (50 to 200 mg) outpatient trials for MDD (n=373) with another sertraline HCl product, there was a difference in weight change between sertraline HCl and placebo of roughly 1 kg, for both pediatric patients ages 6 to 11 and pediatric patients ages 12 to 17, in both age groups representing a slight weight loss for the sertraline HCl group compared to a slight gain for the placebo group. For pediatric patients (ages 6 to 11), about 7% of the sertraline HCl-treated patients had a weight loss greater than 7% of body weight compared to 0% of the placebo-treated patients; for pediatric patients (ages 12 to 17), about 2% of sertraline HCl-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 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 HCl treatment (10 weeks in a placebo-controlled trial + 24 weeks open-label, n=68) 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 HCl on the growth, development, and maturation in pediatric patients.

Juvenile Animal Toxicity 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 to 17 years of age) receiving the maximum recommended dose of sertraline (200 mg/day).

8.5 Geriatric Use

Of the total number of patients with MDD, OCD, and other conditions in clinical studies with another sertraline product, 797 (17%) were ≥ 65 years old, 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 another sertraline HCl product in MDD placebo-controlled trials, the overall profile of adverse reactions was generally similar to that shown in Table 2 [see *Adverse Reactions (6.1)*], except for tinnitus, arthralgia with an incidence of at least 2% and at a rate greater than placebo in geriatric patients.

SSRIs, including sertraline HCl, 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

Sertraline HCl Capsules are not recommended in patients with mild (Child-Pugh score 5 or 6), moderate (Child-Pugh score 7 to 10), or severe (Child-Pugh score 10 to 15) hepatic impairment. The effect of Sertraline HCl Capsules in patients with mild, moderate, or severe hepatic impairment was not studied.

Sertraline plasma exposure was higher in patients with mild hepatic impairment, compared with those with normal hepatic function [see *Clinical Pharmacology (12.3)*].

Dosage adjustments are not possible with the available strengths of Sertraline HCl Capsules.

8.7 Renal Impairment

No dose adjustment is necessary in patients with mild (eGFR 60 to 89 mL/minute/1.73 m²), moderate (eGFR 30 to 59 mL/minute/1.73 m²), or severe renal impairment (eGFR 15 to 29 mL/minute/1.73 m²). 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 HCl Capsules contain sertraline, which is not a controlled substance.

9.2 Abuse

In a placebo-controlled, double-blind, randomized study of the comparative abuse liability of another sertraline HCl product, alprazolam, and d-amphetamine in humans, sertraline HCl 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

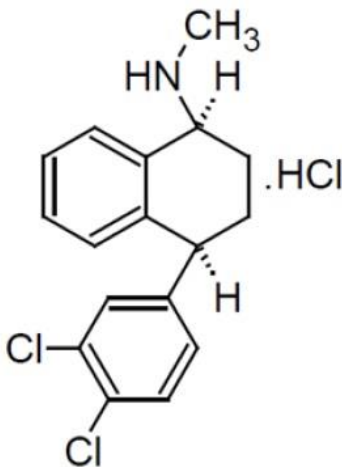
The following have been reported with sertraline HCl tablet overdose:

- 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 overdose 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 overdosage management recommendations.

11 DESCRIPTION

Sertraline HCl Capsules contain sertraline HCl, a selective serotonin reuptake inhibitor (SSRI). Sertraline HCl has a molecular weight of 342.7 and has the following chemical name: (1S,4S)-4-(3,4-dichlorophenyl)-N-methyl-tetralin-1-amine hydrochloride. The empirical formula $C_{17}H_{17}Cl_2N \cdot HCl$ is represented by the following structural formula:



Sertraline HCl is a white to almost white crystalline powder that is slightly soluble in water, acetone and isopropyl alcohol.

Sertraline HCl Capsules is for oral administration and contain 168 mg and 224 mg sertraline HCl, equivalent to 150 mg and 200 mg sertraline, and the following inactive ingredients: croscarmellose sodium, gelatin, hydroxypropyl cellulose, magnesium stearate, microcrystalline cellulose, silicon dioxide and titanium dioxide. The 150 mg capsules contain FD&C Yellow No. 5 as a color additive. The 200 mg capsules contain FD&C Blue No. 1 and FD&C Yellow No. 5 as color additives.

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).

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 no significant affinity for adrenergic (alpha1, alpha2, beta), cholinergic, GABA, dopaminergic, histaminergic, serotonergic (5HT1A, 5HT1B, 5HT2), 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.

Cardiac Electrophysiology

The effect of sertraline on the QTc interval was evaluated in a randomized, double-blind, placebo- and positive-controlled three-period crossover thorough 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 $\Delta\Delta\text{QTc}$ 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* (5.10), *Adverse Reactions* (6), *Drug Interactions* (7.1), *Overdosage* (10)].

12.3 Pharmacokinetics

Absorption

Following a single dose of Sertraline HCl Capsule at 150 mg, the mean peak plasma concentrations (C_{max}) of sertraline occurred between 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 are likely over a range of 150 to 200 mg.

Effect of Food

Administration of Sertraline HCl Capsules with food causes a small increase in C_{max} and AUC.

Distribution

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 ng/mL. However, at up to 300 and 200 ng/mL concentrations, respectively, sertraline and N-desmethylsertraline did not alter the plasma protein binding of two other highly protein bound drugs, warfarin and propranolol.

Elimination

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.

Excretion

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 to 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 to 45% of the administered radioactivity was accounted for in feces, including 12 to 14% unchanged sertraline.

Desmethylsertraline exhibits time-related, dose dependent increases in AUC (0 to 24-hour), C_{max} and C_{min} , with about a 5- to 9-fold increase in these pharmacokinetic parameters between day 1 and day 14.

Specific Populations

Pediatric Patients

Sertraline pharmacokinetics were evaluated in a group of 61 pediatric patients (29 aged 6 to 12 years, 32 aged 13 to 17 years) including both males (N=28) and females (N=33). Relative to the adults, pediatric patients aged 6 to 12 years and 13 to 17 years showed about 22% lower AUC (0-24 hr) and C_{max} values when plasma concentration was adjusted for weight. The half-life was 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 another sertraline HCl product for 14 days was approximately 40% lower than in a similarly studied group of younger (25 to 32 year old) individuals. Steady-state, therefore, was achieved after 2 to 3 weeks in older patients. The same study showed a decreased clearance of desmethylsertraline in older males, but not in older females [see *Use in Specific Populations (8.5)*].

Patients with Hepatic 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 7-8) who received 50 mg of another sertraline HCl product 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 in patients with moderate and severe hepatic impairment have not been studied [see *Use in Specific Populations (8.6)*].

Patients with Renal Impairment

Sertraline is extensively metabolized and excretion of unchanged drug in urine is a minor route of elimination. In volunteers with mild to moderate (CL_{cr} =30-60 mL/min), moderate to severe (CL_{cr} =10-29 mL/min) or severe (receiving hemodialysis) renal impairment (N=10 each group), the pharmacokinetics and protein binding of 200 mg sertraline per day maintained for 21 days were not altered compared to age-matched volunteers (N=12) with no renal impairment. Thus, sertraline multiple dose pharmacokinetics appear to be unaffected by renal impairment [see *Use in Specific Populations (8.7)*].

Drug Interaction Studies

Pimozide

In a controlled study of a single dose (2 mg) of pimozide, 200 mg of another sertraline HCl product (once daily) co-administration to steady state was associated with a mean increase in pimozide AUC and C_{max} 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. 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, and most tricyclic antidepressant drugs) inhibit the biochemical activity of the drug metabolizing isozyme CYP2D6 (debrisoquin hydroxylase), and, thus, may increase the plasma concentrations of co-administered 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 at lower doses has a less prominent inhibitory effect on 2D6 than some others in the class. Nevertheless, even sertraline has the potential for clinically important 2D6 inhibition [see *Drug Interactions* (7.1)].

Phenytoin

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

Cimetidine

In a study assessing disposition of sertraline (100 mg) on the second of 8 days of cimetidine administration (800 mg daily), there were increases in sertraline mean AUC (50%), C_{max} (24%) and half-life (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 (50 to 200 mg/day escalating dose) or placebo, there was a 32% decrease relative to baseline in diazepam clearance for the sertraline group compared to a 19% decrease relative to baseline for the placebo group ($p < 0.03$). There was a 23% increase in T_{max} for desmethyldiazepam in the sertraline 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 another sertraline HCl product 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 another sertraline HCl product 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 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 (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 another sertraline HCl product 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 was co-administered with CYP3A4 substrates, terfenadine, carbamazepine, or cisapride under steady-state conditions. The results of these studies indicated

that sertraline did not increase plasma concentrations of terfenadine, carbamazepine, or cisapride. These data indicate that sertraline's extent of inhibition of CYP3A4 activity is not likely to be of clinical significance. Results of the interaction study with cisapride indicate that sertraline 200 mg (once daily) induces the metabolism of cisapride (cisapride AUC and C_{max} were reduced by about 35%) [see *Drug Interactions* (7.2)].

Microsomal Enzyme Induction

Preclinical studies have shown sertraline to induce hepatic microsomal enzymes. In clinical studies, sertraline was shown to induce hepatic enzymes minimally as determined by a small (5%) but statistically significant decrease in antipyrine half-life following administration of 200 mg of sertraline per day for 21 days. This small change in antipyrine 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/m² basis. There was a dose-related increase of liver adenomas in male mice receiving sertraline at 10 to 40 mg/kg (0.25 to 1.0 times the MRHD on a mg/m² 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/m² basis); this was not accompanied by thyroid hyperplasia. While there was an increase in uterine adenocarcinomas in rats receiving sertraline at 10 to 40 mg/kg (0.5 to 2.0 times the MRHD on a mg/m² 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 (approximately 4 times the maximum recommended human dose on a mg/m² basis in adults).

14 CLINICAL STUDIES

14.1 Major Depressive Disorder

The efficacy of Sertraline HCl Capsules for the treatment of major depressive disorder (MDD) in adult patients is based upon adequate and well-controlled studies of another sertraline HCl product (referred to as "sertraline" in this section). The results of these adequate and well-controlled studies of sertraline are presented below.

The efficacy of sertraline 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)

criteria for MDD (studies MDD-1 and MDD-2).

- Study MDD-1 was an 8-week, 3-arm study with flexible dosing of sertraline, amitriptyline, and placebo. Adult patients received sertraline (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 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 to be superior to placebo on the Hamilton Rating Scale for Depression (HAM-D-17) and the Clinical Global Impression Severity (CGI-S) of Illness and Global Improvement (CGI-I) scores. 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 50 to 200 mg/day. These patients (n=295) were randomized to continuation on double-blind sertraline 50 to 200 mg/day or placebo for 44 weeks. A statistically significantly lower relapse rate was observed for patients taking sertraline compared to those on placebo: sertraline [n=11 (8%)] and placebo [n=31 (39%)]. The mean sertraline dose for completers was 70 mg/day.

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

14.2 Obsessive-Compulsive Disorder

The efficacy of Sertraline HCl Capsules for the treatment of OCD in adults and pediatric patients ages 6 to 17 years is based upon adequate and well-controlled studies of another sertraline HCl product (referred to as “sertraline” in this section). The results of these adequate and well-controlled studies of sertraline are presented below.

Adults with OCD

The effectiveness of sertraline in the treatment of OCD was demonstrated in three multicenter placebo-controlled studies of adult (age 18 to 65) non-depressed outpatients (Studies OCD-1, OCD-2, and OCD-3). Patients in all three studies had moderate to severe OCD (DSM-III 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 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 (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) and -1.48 (placebo).
- Study OCD-2 was a 12-week randomized, placebo-controlled fixed-dose study, including sertraline doses of 50, 100, and 200 mg/day. Sertraline (N=240) was titrated to the assigned dose over two weeks in 50 mg increments every 4 days. Patients receiving sertraline 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 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 in a range of 50 to 200 mg/day; the mean dose for completers was 185 mg/day. Sertraline (N=241) was

titrated to the assigned dose over two weeks in 50 mg increments every 4 days. Patients receiving sertraline 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) and -3.6 (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 was studied in the risk reduction of OCD relapse. In Study OCD-4, patients ranging in age from 18 to 79 meeting DSM-III-R criteria for OCD who had responded during a 52-week single-blind trial on sertraline 50 to 200 mg/day (n=224) were randomized to continuation of sertraline 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 single-blind phase was defined as a decrease in the Y-BOCS score of $\geq 25\%$ 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 and 2, and condition 3 being met at visit 3):

- Condition 1: Y-BOCS score increased by ≥ 5 points, to a minimum of 20, relative to baseline;
- Condition 2: CGI-I increased by $\geq$ one point; and
- Condition 3: Worsening of the patient's condition in the investigator's judgment, to justify alternative treatment.

Patients receiving continued sertraline 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 (ages 6 to 17 years) with OCD

The effectiveness of sertraline for the treatment of OCD was demonstrated in a 12-week, multicenter, placebo-controlled, parallel group study in a pediatric outpatient population (ages 6 to 17) (Study OCD-5). Sertraline (N=92) was initiated at doses of either 25 mg/day (pediatric patients ages 6 to 12) or 50 mg/day (pediatric patients ages 13 to 17), and then titrated at 3 and 4 day intervals (25 mg incremental dose for pediatric patients ages 6 to 12) or 1 week intervals (50 mg incremental dose for pediatric patients ages 13 to 17) over the next four weeks to a maximum dose of 200 mg/day, as tolerated. The mean dose for completers was 178 mg/day. Dosing was once a day in the morning or evening. Patients in this study had moderate to severe OCD (DSM-III-R) with mean baseline ratings on the Children's Yale-Brown Obsessive-Compulsive Scale (CY-BOCS) total score of 22. Patients receiving sertraline experienced a mean reduction of approximately 7 units on the CY-BOCS total score which was statistically significantly greater than the 3 unit reduction for placebo patients (n=95). Analyses for age and gender effects on outcome did not suggest any differential responsiveness on the basis of age or sex.

16 HOW SUPPLIED/STORAGE AND HANDLING

Sertraline HCl Capsules are supplied as:

150 mg Capsules: Hard shell capsules, with "ALM" printed axially on the opaque yellow cap and "664" printed axially on the opaque white body.

NDC 52427-664-30 Bottles of 30

200 mg Capsules: Hard shell capsules, with "ALM" printed axially on the opaque yellowish green cap and "672" printed axially on the opaque white body.

NDC 52427-672-30 Bottles of 30

Store at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) [See USP Controlled Room Temperature].

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Suicidal Thoughts and Behaviors

Advise patients and caregivers to look for the emergence of suicidality, especially early during treatment and when the dosage is adjusted up or down, and instruct them to report such symptoms to the healthcare provider [see *Boxed Warning and Warnings and Precautions (5.1)*].

Serotonin Syndrome

Caution patients about the risk of serotonin syndrome, particularly with the concomitant use of Sertraline HCl Capsules with other serotonergic drugs including triptans, tricyclic antidepressants, opioids, lithium, tryptophan, buspirone, amphetamines, St. John's Wort, and with drugs that impair metabolism of serotonin (in particular, MAOIs, both those intended to treat psychiatric disorders and also others, such as linezolid). Instruct patients to contact their health care provider or report to the emergency room if they experience signs or symptoms of serotonin syndrome [see *Warnings and Precautions (5.2)*, *Drug Interactions (7.1)*].

Increased Risk of Bleeding

Inform patients about the concomitant use of Sertraline HCl Capsules with aspirin, NSAIDs, other antiplatelet drugs, warfarin, or other anticoagulants because the combined use has been associated with an increased risk of bleeding. Advise patients to inform their health care providers if they are taking or planning to take any prescription or over-the-counter medications that increase the risk of bleeding [see *Warnings and Precautions (5.3)*].

Activation of Mania or Hypomania

Advise patients and their caregivers to observe for signs of activation of mania/hypomania and instruct them to report such symptoms to the healthcare provider [see *Warnings and Precautions (5.4)*].

Discontinuation Syndrome

Advise patients not to abruptly discontinue Sertraline HCl Capsules and to discuss any tapering regimen with their healthcare provider. Inform patients that adverse reactions can occur when Sertraline HCl Capsules is discontinued [see *Warnings and Precautions (5.5)*].

Sexual Dysfunction

Advise patients that use of Sertraline HCl Capsules may cause symptoms of sexual dysfunction in both male and female patients. Inform patients that they should discuss any changes in sexual function and potential management strategies with their healthcare provider [see *Warnings and Precautions (5.12)*].

Allergic Reactions and Reactions to FD&C Yellow No. 5 (Tartrazine)

Advise patients to notify their healthcare provider if they develop an allergic reaction such as rash, hives, swelling, or difficulty breathing [see *Adverse Reactions (6.2)*].

Advise patients that Sertraline HCl Capsules contain FD&C Yellow No. 5 (tartrazine), which may cause allergic-type reactions (including bronchial asthma) in certain susceptible persons or in patients who also have an aspirin hypersensitivity [*see Warnings and Precautions (5.11)*].

Pregnancy

Advise women to notify their healthcare provider if they are pregnant or are planning to become pregnant during treatment with Sertraline HCl Capsules. Advise women that there is a pregnancy exposure registry that monitors pregnancy outcomes of women exposed to Sertraline HCl Capsules during pregnancy.

Inform women that Sertraline HCl Capsules may cause withdrawal symptoms in the newborn or persistent pulmonary hypertension of the newborn (PPHN) [*see Use in Specific Populations (8.1)*].

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