PRODUCT MONOGRAPH

[Pr] ratio-SERTRALINE

(Sertraline Hydrochloride Capsules)

25 mg, 50 mg & 100 mg

Antidepressant/Antipanic/Antiobsessional Agent

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[Pr] ratio-SERTRALINE

(Sertraline hydrochloride)

25 mg, 50 mg & 100 mg capsules

THERAPEUTIC CLASSIFICATION

Antidepressant/Antipanic/Antiobsessional Agent

ACTION

The mechanism of action of sertraline is presumed to be linked to its ability to inhibit the neuronal re-uptake of serotonin. It has only very weak effects on norepinephrine and dopamine neuronal reuptake. At clinical doses, sertraline blocks the uptake of serotonin into human platelets.

Like most clinically effective antidepressants, sertraline down regulates brain norepinephrine and serotonin receptors in animals. In receptor binding studies, sertraline has no significant affinity for adrenergic (*alpha*$_1$, *alpha*$_2$, & *beta*), cholinergic, GABA, dopaminergic, histaminergic, serotonergic (5- HT1 A, 5-HT1B, 5-HT2) or benzodiazepine binding sites.

In placebo-controlled studies in normal volunteers, sertraline hydrochloride capsules did not cause sedation and did not interfere with psychomotor performance.

Pharmacokinetics:

Following multiple oral once-daily doses of 200 mg, the mean peak plasma concentration (C_{max}) of sertraline is 0.19 μg/mL occurring between 6 to 8 hours post-dose. The area under the plasma

concentration time curve is 2.8 mg hr/l. For desmethylsertraline, C_{max} is 0.14 μg/mL, the half-life 65 hours and the area under the curve 2.3 mg hr/l. Following single or multiple oral once-daily doses of 50 to 400 mg/day the average terminal elimination half-life is approximately 26 hours. Linear dose proportionality has been demonstrated over the clinical dose range of 50 to 200 mg/day.

Food appears to increase the bioavailability by about 40%: it is recommended that Sertraline hydrochloride capsules be administered with meals.

Sertraline is extensively metabolized to N-desmethylsertraline, which shows negligible pharmacological activity. Both sertraline and N-desmethylsertraline undergo oxidative deamination and subsequent reduction, hydroxylation and glucuronide conjugation. Biliary excretion of metabolites is significant. Approximately 98% of sertraline is plasma protein bound. The interactions between sertraline and other highly protein bound drugs have not been fully evaluated. (See **PRECAUTIONS** section).

The pharmacokinetics of sertraline itself appear to be similar in young and elderly subjects. Plasma levels of N-desmethylsertraline show a 3-fold elevation in the elderly following multiple dosing, however, the clinical significance of this observation is not known.

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

Liver and Renal Disease: The pharmacokinetics of sertraline in patients with significant hepatic or renal dysfunction have been determined. (See **PRECAUTIONS** and **DOSAGE** AND **ADMINISTRATION** sections)

Clinical Trials

Panic Disorder: Four placebo-controlled clinical trials have been performed to investigate the efficacy of sertraline in panic disorder: two flexible dose studies and two fixed dose studies. At the

last week of treatment (week 10 or 12), both flexible dose studies and one of the fixed dose studies showed statistically significant differences from placebo in favour of sertraline in terms of mean change from baseline in the total number of full panic attacks (last observation carried forward analysis). As the flexible dose studies were of identical protocol, data for these investigations can be pooled. The mean number of full panic attacks at baseline was 6.2/week (N=167) in the sertraline group and 5.4/week in the placebo group (N=175). At week 10 (last observation carried forward analysis), the mean changes from baseline were -4.9/week and -2.5/week for the sertraline and placebo groups, respectively. The proportion of patients having no panic attacks at the final evaluation was 57% in the placebo group and 69% in the sertraline group. The mean daily dose administered at the last week of treatment was approximately 120 mg (range: 25-200 mg) in the flexible dose studies. No clear dose-dependency has been demonstrated over the 50 to 200 mg/day dose range investigated in the fixed dose studies.

Obsessive-Compulsive Disorder: Five placebo-controlled clinical trials, in adults, of 8 to 16 weeks in duration have been performed to investigate the efficacy of sertraline in obsessive-compulsive disorder: four flexible dose studies (50-200 mg/day) and one fixed dose study (50, 100, & 200 mg/day). Results for three of the four flexible dose studies and the 50 and 200 mg dose groups of the fixed dose study were supportive of differences from placebo in favour of sertraline in terms of mean change from baseline to endpoint on the Yale-Brown Obsessive-Compulsive Scale and/or the National Institute of Mental Health Obsessive-Compulsive Scale (last observation carried forward analysis). No clear dose-dependency was demonstrated over the 50 to 200 mg/day dose range investigated in the fixed dose studies. In the flexible dose studies, the mean daily dose administered at the last week of treatment ranged from 124-180 mg.

One placebo-controlled clinical trial of 12 weeks duration, was performed in children and adolescents aged 6-17 years, to investigate the efficacy of sertraline in obsessive-compulsive disorder. The study used flexible dosing, starting with 25 mg/day in children 6-12 years old (sertraline n=53, placebo n=54) and with 50 mg/day in adolescents 13-17 years old (sertraline n=39, placebo n=41). In both age groups, sertraline was titrated up to a maximum 200 mg/day, over 4

weeks, as tolerated. The mean dose for completers (74/92 sertraline treated patients) was 178 mg/day. Results showed statistically significant differences from placebo in favour of sertraline in terms of mean change from baseline to endpoint (last observation carried forward analysis) on the Children's Yale-Brown Obsessive Compulsive Scale (p=0.005), the National Institute of Mental Health Obsessive-Compulsive Scale (p=0.019) and the Clinical Global Impression Improvement Rating Scale (p=0.002).

The long term safety, including effects on growth and development, in patients under 18 years of age, has not been established.

A comparative bioavailability study was performed in the fasting state to compare the pharmacokinetic parameters of **ratio-SERTRALINE** 100 mg capsules (ratiopharm inc.) versus ZOLOFT 100 mg capsules (Pfizer Inc.). The results of the study are shown in the following tables.

SUMMARY TABLE OF THE COMPARATIVE BIOAVAILABILITY DATA of ratio-SERTRALINE 100 mg capsules (ratiopharm inc., Lot # P-0370)

Versus

ZOLOFT 100 mg capsules (Pfizer Inc., Canada, Lot # 902-72201)

A single 100 mg (1 x 100 mg capsule) oral administration in the fasting state

Measured Data

Parameter	Geometric Mean Arithmetic Mean (CV%)		Ratio of Geometric Mean (90% Confidence Limit)
	Test	Reference	
AUC_{0-72h} (ng/h/mL)	511.20 551.39 (42.88)	587.66 627.20 (39.57)	87 (82 to 92)
AUC_{∞} (ng/h/mL)	593.78 646.44 (46.47)	685.34 740.75 (43.60)	87 (81 to 92)
C_{max} (ng/mL)	19.27 20.79 (41.30)	22.88 24.07 (33.21)	84
T_{max} (h)	8.26 (12.76)	7.61 (16.69)	--
$T_{1/2el}$ (h)	24.21 (20.13)	24.88 (21.57)	-

For T_{max} and $T_{1/2el}$, the arithmetic mean only is presented

STATISTICAL ANALYSIS

PARAMETER	POTENCY CORRECTED RATIO (%)* 90% CI			MEASURED DATA RATIO (%)*90% CI
AUC_{0-72h} (T/R)**	89	84 to 94	87	82 to 92
AUC_{∞} (T/R)	89	83 to 95	87	81 to 92
C_{max} (T/R)	86	--	84	--

*Based on the geometric mean

**Test/Reference

INDICATIONS

Depression:

ratio-SERTRALINE (sertraline hydrochloride) is indicated for the symptomatic relief of depressive illness. However, the antidepressant action of Sertraline hydrochloride in hospitalized depressed patients has not been adequately studied. A placebo-controlled European study carried out over 44 weeks, in patients who were responders to sertraline hydrochloride has indicated that sertraline hydrochloride may be useful in continuation treatment, suppressing re-emergence of depressive symptoms.

However, because of methodological limitations, these findings on continuation treatment have to be considered tentative at this time.

Panic Disorder:

ratio-SERTRALINE is indicated for the symptomatic relief of panic disorder, with or without agoraphobia. The efficacy of sertraline hydrochloride was established in 10-week and 12-week controlled trials of patients with panic disorder as defined according to DSM-III-R criteria.

The effectiveness of sertraline hydrochloride in long-term use for the symptomatic relief of panic disorder (i.e., for more than 12 weeks) has not been systematically evaluated in placebo-controlled trials. Therefore, the physician who elects to use sertraline hydrochloride for extended periods should periodically reevaluate the long-term usefulness of the drug for the individual patient.

Obsessive-Compulsive Disorder:

ratio-SERTR5ALINE is indicated for the symptomatic relief of obsessive-compulsive disorder (OCD). The obsessions or compulsions must be experienced as intrusive, markedly distressing, time-consuming, or significantly interfering with the person's social or occupational functioning. The effectiveness of sertraline hydrochloride in long term use for the symptomatic relief of OCD (i.e., for more than 12 weeks) has not been systematically evaluated in placebo controlled trials. Therefore, the physician who elects to use sertraline hydrochloride for extended periods should periodically reevaluate the long-term usefulness of the drug for the individual patient.

CONTRAINDICATIONS

Sertraline hydrochloride capsules is contraindicated in patients with known hypersensitivity to the drug.

Monoamine Oxidase Inhibitors:

Cases of serious, sometimes fatal, reactions have been reported in patients receiving Sertraline hydrochloride capsules in combination with a monoamine oxidase inhibitor (MAOI), including the selective MAOI, selegiline and the reversible MAOI (reversible inhibitor of monoamine oxidase - RIMA), moclobemide. Some cases presented with features resembling the serotonin syndrome. Similar cases, have been reported with other antidepressants during combined treatment with an MAOI and in patients who have recently discontinued an antidepressant and have been started on an MAOI. Symptoms of a drug interaction between an SSRI and an MAOI include: hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, mental status changes that include confusion, irritability, and extreme agitation progressing to delirium and coma. Therefore, Sertraline hydrochloride should not be used in combination with an MAOI, or within 14 days of discontinuing treatment with an MAOI. Similarly, at least 14 days should elapse after discontinuing Sertraline hydrochloride treatment before starting an MAOI.

Pimozide:

The concomitant use of Sertraline hydrochloride and pimozide is contraindicated as Sertraline hydrochloride has been shown to increase plasma pimozide levels. Elevation of pimozide blood concentration may result in QT interval prolongation and severe arrhythmias including Torsade de Pointes. (See **PRECAUTIONS** and **INFORMATION FOR THE CONSUMER** sections.)

WARNINGS

POTENTIAL ASSOCIATION WITH BEHAVIORAL AND EMOTIONAL CHANGES, INCLUDING SELF-HARM.

Pediatrics: Placebo-Controlled Clinical Trial Data

- **Recent analyses of placebo-controlled clinical trial safety databases from SSRIs and other newer anti-depressants suggest that use of these drugs in patients under the age of 18 may be associated with behavioral and emotional changes, including an increased risk of suicidal ideation and behavior over that of placebo.**

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

Adults and Pediatrics: Additional data

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

Rigorous clinical monitoring for suicidal ideation or other indicators of potential for suicidal behaviour is advised in patients of all ages. This includes monitoring for agitation-type emotional and behavioral changes.

Discontinuation Symptoms

Patients currently taking ratio-SERTRALINE should NOT be discontinued abruptly, due to risk of discontinuation symptoms. At the time that a medical decision is made to discontinue an

SSRI or other newer anti-depressant drug, a gradual reduction in the dose rather than an abrupt cessation is recommended.

Monoamine Oxidase Inhibitors: (See **CONTRAINDICATIONS** section.)

PRECAUTIONS

Activation of Mania/Hypomania:

During clinical testing in depressed patients, hypomania or mania occurred in approximately 0.6% of Sertraline hydrochloride treated patients. Activation of mania/hypomania has also been reported in a small proportion of patients with Major Affective Disorder treated with other marketed antidepressants.

Seizure:

Sertraline hydrochloride has not been evaluated in patients with seizure disorders. These patients were excluded from clinical studies during the product's premarket testing. No seizures were observed among approximately 3000 patients treated with sertraline hydrochloride in the development program for depression. However, 4 patients out of approximately 1800 (220 < 18 years of age) exposed during the development program for obsessive-compulsive disorder experienced seizures representing a crude incidence of 0.2%. Three of these patients were adolescents, two with a seizure disorder and one with a family history of seizure disorder, none of whom were receiving anticonvulsant medication. Accordingly, Sertraline hydrochloride capsules should be introduced with care in patients with a seizure disorder.

Suicide:

The possibility of a suicide attempt is inherent in depression and may persist until significant remission occurs. Therefore, high risk patients should be closely supervised throughout therapy and consideration should be given to the possible need for hospitalization. It should be noted that a causal role for SSRIs and other newer anti-depressants in inducing self-harm or harm to others has not been established. In order to minimize the opportunity for overdosage, prescriptions for Sertraline hydrochloride should be written for the smallest quantity of drug consistent with good patient management. (See WARNINGS: POTENTIAL ASSOCIATION WITH BEHAVIORAL AND EMOTIONAL CHANGES, INCLUDING SELF-HARM).

Because of the well-established co-morbidity between both obsessive-compulsive disorder and

depression and panic disorder and depression, the same precautions should be observed when treating patients with obsessive-compulsive disorder and panic disorder.

Discontinuation of Treatment with Sertraline hydrochloride:

When discontinuing treatment, patients should be monitored for symptoms which may be associated with discontinuation (e.g. dizziness, abnormal dreams, sensory disturbances (including paresthesias and electric shock sensations), agitation, anxiety, fatigue, confusion, headache, tremor, nausea, vomiting and sweating or other symptoms which may be of clinical significance (see ADVERSE REACTIONS). A gradual reduction in the dosage over several weeks, rather than abrupt cessation is recommended whenever possible. If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, dose titration should be managed on the basis of the patient's clinical response. (See ADVERSE REACTIONS and DOSAGE AND ADMINISTRATION sections).

Occupational Hazards:

Any psychoactive drug may impair judgment, thinking, or motor skills, and patients should be advised to avoid driving a car or operating hazardous machinery until they are reasonably certain that the drug treatment does not affect them adversely.

Use in Patients with Concomitant Illness:

General: Clinical experience with Sertraline hydrochloride capsules in patients with certain concomitant systemic illnesses is limited. Caution is advisable in using Sertraline hydrochloride capsules in patients with diseases or conditions that could affect metabolism or hemodynamic responses.

Cardiovascular Conditions:

Sertraline hydrochloride capsules has not been evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or unstable heart disease. However, the electrocardiograms of 1006 patients who received Sertraline hydrochloride capsules in double-blind trials were evaluated and the data indicate that Sertraline hydrochloride capsules is not associated

with the development of clinically significant ECG abnormalities.

In placebo-controlled trials, the frequency of clinically noticeable changes (± 15-20 mmHg) in blood pressure was similar in patients treated with either Sertraline hydrochloride or placebo.

Hepatic Dysfunction:

Sertraline is extensively metabolized by the liver. A single dose pharmacokinetic study in subjects with mild, stable cirrhosis demonstrated a prolonged elimination half-life and increased AUC in comparison to normal subjects. The use of sertraline in patients with hepatic disease must be approached with caution. If sertraline is administered to patients with hepatic impairment, a lower or less frequent dose should be considered. (See ACTION and DOSAGE AND ADMINISTRATION sections).

Renal Dysfunction:

Sertraline hydrochloride is extensively metabolized and excretion of unchanged drug in the urine is a minor route of elimination.

In patients with mild to moderate renal impairment (creatinine clearance 30-60 ml/min) or moderate to severe renal impairment (creatinine clearance 10-29 ml/min), multiple-dose pharmacokinetic parameters (AUC0-24 or Cmax) were not significantly different compared with controls. Half-lives were similar and there were no differences in plasma protein binding in all groups studied. This study indicates that, as expected from the low renal excretion of sertraline, sertraline dosing does not have to be adjusted based on the degree of renal impairment.

Carcinogenesis:

In carcinogenicity studies in CD-1 mice, sertraline at doses up to 40 mg/kg produces a dose related increase in the incidence of liver adenomas in male mice. Liver adenomas have a very variable rate of spontaneous occurrence in the CD-1 mouse. The clinical significance of these findings is unknown.

Use in Pregnancy and Nursing Mothers:

The safety of Sertraline hydrochloride during pregnancy and lactation has not been established and therefore, it should not be used in women of childbearing potential or nursing mothers, unless, in the opinion of the physician, the potential benefits to the patient outweigh the possible hazards to the fetus.

Post-marketing reports indicate that some neonates exposed to Sertraline hydrochloride, SSRIs (Selective Serotonin Reuptake Inhibitors), or other newer antidepressants late in the third trimester have developed complications requiring prolonged hospitalization, respiratory support, and tube feeding. Such complications can arise immediately upon delivery. Reported clinical findings have included respiratory distress, cyanosis, apnea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycemia, hypotonia, hypertonia, hyperreflexia, tremor jitteriness, irritability and constant crying. These features are consistent with either a direct toxic effect of SSRIs and other newer antidepressants, or possibly, a drug discontinuation syndrome. It should be noted that, in some cases, the clinical picture is consistent with serotonin syndrome (see PRECAUTIONS-Monoamine Oxidase Inhibitors). When treating a pregnant woman with SERTRALINE during the third trimester, the physician should carefully consider the potential risks and benefits of treatment. (See DOSAGE AND ADMINISTRATION section).

Labor and Delivery:

The effect of Sertraline hydrochloride on labor and delivery in humans is unknown.

Use in Children:

The safety and effectiveness of Sertraline hydrochloride in children below the age of 18 have not been established.

Use in Elderly:

462 elderly patients (≥ 65 years) with depressive illness have participated in multiple dose therapeutic studies with Sertraline hydrochloride. The pattern of adverse reactions in the elderly was comparable to that in younger patients.

Hyponatremia:

Several cases of hyponatremia have been reported and appeared to be reversible when sertraline was discontinued. Some cases were possibly due to the syndrome of inappropriate antidiuretic hormone secretion. The majority of these occurrences have been in elderly individuals, some in patients taking diuretics or who were otherwise volume depleted.

Platelet Function:

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

Interactions:

CNS Active Drugs:

Sertraline hydrochloride capsules (200 mg daily) did not potentiate the effects of carbamazepine, haloperidol or phenytoin on cognitive and psychomotor performance in healthy subjects, however the risk of using Sertraline hydrochloride in combination with other CNS active drugs has not been systematically evaluated. Consequently, caution is advised if the concomitant administration of Sertraline hydrochloride and such drugs is required.

Pimozide:

In a controlled study of a single dose (2 mg) of pimozide, 200 mg sertraline (q.d.) co-administration to steady state was associated with a mean increase in pimozide AUC and Cmax of about 40%. Although these increases were not identified in the trial as being associated with clinically important effects on QT intervals, the trial design was not optimal for the investigation of pharmacodynamic effects in the clinical setting. For ethical considerations, a trial with higher doses could not be done. Since the highest recommended pimozide dose (12 mg) has not been evaluated in combination with sertraline, the effect on QT interval and PK parameters at doses higher than 2 mg at this time are not known. While the mechanism of this interaction is unknown, due to the narrow therapeutic index of pimozide and due to the interaction noted at a low dose of pimozide, concomitant administration of Sertraline hydrochloride and pimozide is contraindicated (see CONTRAINDICATIONS and INFORMATION FOR THE CONSUMER sections).

Serotonergic Drugs:

There is limited controlled experience regarding the optimal timing of switching from other antidepressants and antipanic agents to sertraline. Care and prudent medical judgment should be exercised when switching, particularly from long-acting agents. The duration of washout period which should intervene before switching from one selective serotonin reuptake inhibitor (SSRI) or Tricyclic Antidepressants (TCAs) etc. to another has not been established.

Co-administration with tryptophan, TCAs and others antidepressants may lead to a high incidence of serotonin-associated side effects.

Rare postmarketing reports describe patients with weakness, hyperreflexia, and incoordination following the combined use of a selective serotonin reuptake inhibitor (SSRI) and 5-HT1 agonists (triptans). If concomitant treatment with Sertraline hydrochloride and a triptan (e.g., almotriptan, sumatriptan, rizatriptan, naratriptan, zolmitriptan), tricyclic antidepressants, or other drugs with serotonergic activity (including but not limited to fenfluramine and tryptophan) is clinically warranted and appropriate observation of the patient for acute and long-term adverse events is advised.

St. John's Wort:

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

Lithium:

In placebo-controlled trials in normal volunteers, the co-administration of sertraline with lithium did not significantly alter lithium pharmacokinetics, but did result in an increase in tremor relative to placebo, indicating a possible pharmacodynamic interaction. When co-administering sertraline with medications, such as lithium, which may act via serotonergic mechanisms, patients should be appropriately monitored.

Phenytoin:

It is recommended that plasma phenytoin concentrations be monitored following initiations of sertraline therapy, with appropriate adjustments to the phenytoin dose. The pharmacokinetic and pharmacodynamic effects have not been adequately characterized.

Monoamine Oxidase Inhibitors - See **CONTRAINDICATIONS** section.

Drugs Metabolized by P450 System:

Drugs Metabolized by P450 3A4:

In two separate *in vivo* interaction studies, sertraline was co-administered with cytochrome P450 3A4 substrates, terfenadine or carbamazepine, under steady-state conditions. The results of these studies demonstrated that sertraline co-administration did not increase plasma concentrations of terfenadine or carbarnazepine. These data suggest that sertraline's extent of inhibition of P450 3A4 activity is not likely to be of clinical significance.

Drugs Metabolized by P450 2D6:

Many antidepressants, e.g., the SSRls, including sertraline and most tricyclic antidepressants, inhibit

the biochemical activity of the drug metabolizing isozyme, cytochrome P450 2D6 (debrisoquin hydroxylase), and thus may increase the plasma concentration of co-administered drugs that are metabolized primarily by 2D6 and which have a narrow therapeutic index, e.g., the tricyclic antidepressants and the type Ic antiarrhythmics, propafenone and flecainide. There is variability among the antidepressants in the extent of clinically important P450 2D6 inhibition. In two drug interaction clinical trials using desipramine and the recommended starting SSRI doses in normal volunteers, the effect of Sertraline hydrochloride was compared to two other SSRIs. In the first study, mean desipramine steady state AUC (24) increased by 23% and 380% during co-administration with Sertraline hydrochloride and the comparative SSRI, respectively. In a second study using a different comparative SSRI, mean desipramine steady state AUC (24) increased by 37% and 421% during co-administration with Sertraline hydrochloride and the comparative SSRI, respectively. These trial results indicate that the effect of Sertraline hydrochloride was significantly less pronounced than that of the two comparative SSRIs. Nevertheless, concomitant use of a drug metabolized by P450 2D6 with Sertraline hydrochloride, may require lower doses than are usually prescribed for the other drug. Furthermore, whenever Sertraline hydrochloride is withdrawn from co-therapy, an increased dose of the co-administered drug may be required.

Electroconvulsive Therapy:

There are no clinical studies with the combined use of electroconvulsive therapy (ECT) and Sertraline hydrochloride.

Alcohol:

Although Sertraline hydrochloride did not potentiate the cognitive and psychomotor effects of alcohol in experiments with normal subjects, the concomitant use of Sertraline hydrochloride and alcohol in depressed, panic disorder or OCD patients has not been studied and is not recommended.

Hypoglycemic Drugs:

There are no controlled clinical trials with Sertraline hydrochloride in diabetic patients treated with insulin or oral hypoglycemic drugs.

In a placebo-controlled trial in normal volunteers, the administration of Sertraline hydrochloride for 22 days (dose of Sertraline hydrochloride was 200 mg/day for the final 13 days), caused a statistically significant 16% decrease in the clearance of tolbutamide following an I.V. dose of 1000 mg. In a placebo-controlled study in normal volunteers, glibenclamide (5 mg) was given before and after administration of sertraline (200 mg/day final dose) to steady state or placebo. No significant changes were observed in the total plasma concentration of glibenclamide.

Hypoglycemia requiring dextrose infusion was observed in one patient treated with Sertraline hydrochloride, glibenclamide, haloperidol, bisacodyl, aspirin and flucloxacillin. The causal relationship to Sertraline hydrochloride treatment was not firmly established. Nevertheless, close monitoring of glycemia in patients treated with Sertraline hydrochloride and oral hypoglycemic drugs or insulin is recommended.

Digoxin:

In a parallel placebo controlled trial in normal volunteers (10 subjects per group), the administration of Sertraline hydrochloride for 17 days (dose of Sertraline hydrochloride: 200 mg for the last 10 days) did not cause changes in the total plasma concentrations of digoxin except a decrease of T_{max} as compared to baseline.

Beta Blockers:

There is no experience with the use of Sertraline hydrochloride in hypertensive patients controlled by beta-blockers. In a placebo-controlled crossover study in normal volunteers, the effect of Sertraline hydrochloride on the ß-adrenergic blocking activity of atenolol was assessed. The mean CD25's (the doses of isoproterenol required to increase heart rate by 25 bpm, the chronotropic dose 25 or CD25) and the average decreases in heart rate seen with atenolol during exercise test were not statistically different in the Sertraline hydrochloride versus the placebo group. These data suggest that Sertraline

hydrochloride does not alter the ß-blocking action of atenolol.

Cimetidine:

In a placebo-controlled crossover study in normal volunteers, the potential of cimetidine to alter the disposition of a single 100 mg dose of Sertraline hydrochloride was assessed. The mean sertraline C_{max} and AUC were significantly higher in the cimetidine-treated group, as were the mean desmethylsertraline T_{max} and AUC. These data suggest that concomitant administration of cimetidine may inhibit the metabolism of sertraline and its metabolite, desmethylsertraline, and may result in a decrease in the clearance and first pass metabolism of sertraline, with a possible increase in drug-related side effects.

Diazepam:

In a normal volunteer, double-blind, placebo-controlled study comparing the disposition of intravenously administered diazepam before and after administration of sertraline (200 mg/day final dose) to steady state or placebo, there was a statistically significant 13% decrease relative to baseline in diazepam clearance for the sertraline group over that of the placebo group. These changes are of unknown clinical significance.

Warfarin:

In a placebo-controlled study in healthy men comparing prothrombin time AUC (0-120 hr) following single dosing with warfarin (0.75 mg/kg) before and after dosing to steady state with either sertraline (200 mg/day final dose) or placebo, there was a statistically significant mean increase in prothrombin time of 8% relative to baseline for sertraline compared to a 1% decrease for placebo. The normalization of prothrombin time for the sertraline group was delayed compared to the placebo group. The clinical significance of these changes are unknown. Accordingly, prothrombin time should be carefully monitored when sertraline therapy is initiated or stopped in patients receiving warfarin.

Because sertraline is highly bound to plasma protein, the administration of Sertraline hydrochloride to a patient taking another drug which is tightly bound to protein may cause a shift in plasma

concentrations potentially resulting in an adverse effect. Conversely adverse effects may result from displacement of protein bound sertraline by other tightly bound drugs.

Microsomal Enzyme Induction:

Sertraline hydrochloride was shown to induce hepatic enzymes as determined by the decrease of the antipyrine half-life. This degree of induction reflects a clinically insignificant change in hepatic metabolism.

Physical and Psychological Dependence:

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. Pre-marketing clinical experience with Sertraline hydrochloride did not reveal any drug-seeking behavior. In animal studies Sertraline hydrochloride does not demonstrate stimulant or barbiturate-like (depressant) abuse potential. As with any CNS active drug, however, physicians should carefully evaluate patients for history of drug abuse and follow such patients closely, observing them for signs of Sertraline hydrochloride misuse or abuse (e.g. development of tolerance, incrementation of dose, drug-seeking behavior).

ADVERSE REACTIONS

Depression:

In clinical development programs, Sertraline hydrochloride has been evaluated in 1902 subjects with depression. The most commonly observed adverse events associated with the use of Sertraline hydrochloride were: gastrointestinal complaints, including nausea, diarrhea/loose stools and dyspepsia; male sexual dysfunction (primarily ejaculatory delay); insomnia and somnolence; tremor; increased sweating and dry mouth; and dizziness. In the fixed dose placebo controlled study, the overall incidence of side effects was dose related with a majority occurring in the patients treated with 200 mg dose.

The discontinuation rate due to adverse events was 15 % in 2710 subjects who received Sertraline hydrochloride in pre-marketing multiple dose clinical trials. The more common events (reported by at least 1 % of subjects) associated with discontinuation included agitation, insomnia, male sexual dysfunction (primarily ejaculatory delay), somnolence, dizziness, headache, tremor, anorexia, diarrhea/loose stools, nausea and fatigue.

Incidence in Controlled Clinical Trials - **TABLE 1** enumerates adverse events that occurred at a frequency of 1 % or more among Sertraline hydrochloride patients who participated in controlled trials comparing titrated Sertraline hydrochloride with placebo.

TABLE 1

TREATMENT-EMERGENT ADVERSE EXPERIENCE INCIDENCE IN PLACEBO-C0NTROLLED CLINICAL TRIALS IN ADULTS*

	Percent of Patients Reporting	
ADVERSE EXPERIENCE	**SERTRALINE (n=861)**	**PLACEBO (n=853)**
Autonomic Nervous System Disorders		
Mouth Dry	16.3	9.3
Sweating Increased	8.4	2.9
Cardiovascular		
Palpitations	3.5	1.6
Chest Pain	1.0	1.6
Centr. & Periph. Nerv. System Disorders		
Headache	20.3	19.0
Dizziness	11.7	6.7
Tremor	10.7	2.7
Paresthesia	2.0	1.8
Hypoesthesia	1.7	0.6
Twitching	1.4	0.1
Hypertonia	1.3	0.4
Disorders of Skin and Appendages		
Rash	2.1	1.5
Gastro-Intestinal Disorders		
Nausea	26.1	11.8
Diarrhea/Loose Stools	17.7	9.3
Constipation	8.4	6.3
Dyspepsia	6.0	2.8
Vomiting	3.8	1.8
Flatulence	3.3	2.5
Anorexia	2.8	1.6
Abdominal Pain	2.4	2.2
Appetite Increased	1.3	0.9
General		
Fatigue	10.6	8.1
Hot Flushes	2.2	0.5
Fever	1.6	0.6
Back Pain	1.5	0.9
Metabolic and Nutritional Disorders		
Thirst	1.4	0.9
Musculo-Skeletal System Disorders		
Myalgia	1.7	1.5
Psychiatric Disorders		
Insomnia	16.4	8.8
Sexual Dysfunction-Male (1)	15.5	2.2

Somnolence	13.4	5.9
Agitation	5.6	4.0
Nervousness	3.4	1.9
Anxiety	2.6	1.3
Yawning	1.9	0.2
Sexual Dysfunction-Female (2)	1.7	0.2
Concentration Impaired	1.3	0.5
Reproduction		
Menstrual Disorder (2)	1.0	0.5
Respiratory System Disorders		
Rhinitis	2.0	1.5
Pharyngitis	1.2	0.9
Special Senses		
Vision Abnormal	4.2	2.1
Tinnitus	1.4	1.1
Taste Perversion	1.2	0.7
Urinary System Disorders		
Micturition Frequency	2.0	1.2
Micturition Disorder	1.4	0.5

* Events reported by at least 1 % of patients treated with sertraline are included.

(1) % based on male patients only: 271 sertraline and 271 placebo patients. Male sexual dysfunction can be broken down into the categories of decreased libido, impotence and ejaculatory delay. In this data set, the percentages of males in the group with these complaints are 4.8%, 4.8% and 8.9%, respectively. It should be noted that since some sertraline patients reported more than one category of male sexual dysfunction, the incidence of each category of male sexual dysfunction combined is larger than the incidence for the general category of male sexual dysfunction, in which each patient is counted only once.

(2) % based on female patient only: 590 sertraline and 582 placebo patients.

Panic Disorder

In placebo-controlled clinical trials, 430 patients with panic disorder were treated with sertraline in doses of 25 - 200 mg/day. During treatment, most patients received doses of 50 - 200 mg/day. Adverse events observed at an incidence of at least 5% for sertraline and at an incidence that was twice or more the incidence among placebo-treated patients included: diarrhea, ejaculation failure (primarily ejaculatory delay), anorexia, constipation, libido decreased, agitation, and tremor.

In the total safety data base for panic disorder, 14% of patients discontinued treatment due to an adverse event. The most common events leading to discontinuation were nausea (2.6%), insomnia

(2.3%), somnolence (2.3%), and agitation (2.1 %).

Obsessive-Compulsive Disorder

In placebo-controlled clinical trials for OCD, adverse events observed at an incidence of at least 5% for sertraline and at an incidence that was twice or more the incidence among placebo-treated patients included: nausea, insomnia, diarrhea, decreased libido, anorexia, dyspepsia, ejaculation failure (primarily ejaculatory delay), tremor, and increased sweating.

In placebo-controlled clinical trials for OCD, 10% of patients treated with sertraline discontinued treatment due to an adverse event. The most common events leading to discontinuation were nausea (2.8%), insomnia (2.6%), and diarrhea (2.1%).

Incidence in Controlled Clinical Trial

TABLE 2 enumerates adverse events that occurred at a frequency of 2% or more among patients on sertraline who participated in controlled trials comparing sertraline with placebo in the treatment of panic disorder and obsessive-compulsive disorder. Only those adverse events which occurred at higher rate during sertraline treatment than during placebo treatment are included.

TABLE 2

TREATMENT-EMERGENT ADVERSE EXPERIENCE INCIDENCE IN PLACEBO-CONTROLLED CLINICAL TRIALS FOR PANIC AND OBSESSIVE-COMPULSIVE DISORDER IN ADULTS*

ADVERSE EXPERIENCE	(Percent of Patients Reporting)			
	PANIC DISORDER		OBSESSIVE COMPULSIVE DISORDER	
	Sertraline (N=430)	Placebo (N=275)	Sertraline (N=533)	Placebo (N=373)
Autonomic Nervous System Disorders				
Mouth Dry	15	10	14	9
Sweating Increased	5	1	6	1
Cardiovascular				
Palpitations	-	-	3	2
Chest Pain	-	-	3	2
Centr. & Periph. Nerv. System Disorders				
Tremor	5	1	8	1
Paresthesia	4	3	3	1
Headache	-	-	30	24
Dizziness	-	-	17	9
Hypertonia	-	-	2	1
Disorders of Skin and Appendages				
Rash	4	3	2	1
Gastrointestinal Disorders				
Nausea	29	18	30	11
Diarrhea	20	9	24	10
Dyspepsia	10	8	10	4
Constipation	7	3	6	4
Anorexia	7	2	11	2
Vomiting	6	3	3	1
Flatulence	-	-	4	1
Appetite Increased	-	-	3	1
General				
Fatigue	11	6	14	10
Hot Flushes	3	1	2	1
Pain	-	-	3	1
Back Pain	-	-	2	1
Metabolic and Nutritional Disorders				
Weight Increase	-	-	3	0
Musculoskeletal System Disorders				
Arthralgia	2	1	-	
Psychiatric Disorders				
Insomnia	25	18	28	12
Somnolence	15	9	15	8
Nervousness	9	5	7	6
Libido Decreased	7	1	11	2
Agitation	6	2	6	3
Anxiety	4	3	8	6
Concentration Impaired	3	0	-	-
Depersonalization	2	1	3	1
Paroniria	-	-	2	1

Respiratory System Disorders				
Pharyngitis	-	-	4	2
Special Senses				
Tinnitus	4	3	-	-
Vision Abnormal	-	-	4	2
Taste Perversion	-	-	3	1
Urogenital				
Ejaculation Failure (1)	19	1	17	2
Impotence (2)	2	1	5	1

* Events reported by at least 2% of patients treated with sertraline hydrochloride are included, except for the following events which had an incidence on placebo greater than or equal to sertraline hydrochloride [Panic Disorder]: headache, dizziness, malaise, abdominal pain, respiratory disorder, pharyngitis, flatulence, vision abnormal, pain, upper respiratory tract infection, and paroniria. [OCD]: abdominal pain, respiratory disorder, depression, and amnesia.

(1) Primarily ejaculatory delay; % based on male patients only: Panic Disorder: 216 sertraline hydrochloride and 134 placebo patients, OCD: 296 sertraline and 219 placebo patients.

(2) % based on male patients only: Panic Disorder: 216 sertraline hydrochloride and 134 placebo patients, OCD: 296 sertraline hydrochloride and 219 placebo patients.

Suicidality-related adverse events from clinical trials in major depressive disorder in the pediatric population

In the safety analysis from controlled clinical trials in children and adolescents with major depressive disorder aged 6 to 17 years, both the number and percentage of patients for whom suicide attempts were reported was the same for the sertraline arm (2/189, 1.1%) as for the placebo arm (2/184, 1.1%), while the corresponding event rates of suicide attempts were 1.1% (2 attempts in 2/189 26 patients) in sertraline-treated patients versus 1.6% in placebo-treated patients (3 attempts in 2/184 patients). For the additional category of "other events possibly related to self-harm", which includes suicidal ideation and self-injurious behaviors such as cutting, event rates were 2.1% (4 events in 189 patients) in sertraline-treated patients and 0% in placebo-treated patients.

Overall, the total reported event rates for both suicide attempts and other events possibly related to self-harm are as follows: 3.2% or 6 /189 for sertraline versus 1.6% or 3/184 for placebo. (See WARNINGS, POTENTIAL ASSOCIATION WITH BEHAVIORAL AND EMOTIONAL CHANGES, INCLUDING SELF-HARM.)

Other events observed during the premarketing evaluation of Sertraline hydrochloride capsules:

During its pre-marketing assessment, multiple doses of Sertraline hydrochloride were administered to 2710 subjects. The conditions and duration of exposure to Sertraline hydrochloride varied greatly, and included (in overlapping categories) clinical pharmacology studies, open and double-blind studies, uncontrolled and controlled studies, inpatient and outpatient studies, fixed-dose and titration studies, and studies for indications other than depression. Untoward events associated with this exposure were recorded by clinical investigators using terminology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse events without first grouping similar types of untoward events into a smaller number of standardized event categories.

All events are included except those already listed in the previous table or in the **PRECAUTIONS** section, and those reported in terms so general as to be uninformative.

It is important to emphasize that although the events reported occurred during treatment with Sertraline hydrochloride, they were not necessarily caused by it.

Autonomic Nervous System Disorders:

Infrequent: flushing, mydriasis, increased saliva, cold clammy skin; Rare: pallor.

Cardiovascular:

Infrequent: postural dizziness, hypertension, hypotension, postural hypotension, edema, dependent edema, periorbital edema, peripheral edema, peripheral ischemia, syncope, tachycardia;

Rare: precordial chest pain, substernal chest pain, aggravated hypertension, myocardial infarction, varicose veins.

Central and Peripheral Nervous System Disorders:

Frequent: confusion; Infrequent: ataxia, abnormal coordination, abnormal gait, hyperesthesia, hyperkinesia, hypokinesia, migraine, nystagmus, vertigo;

Rare: local anesthesia, coma, convulsions, dyskinesia, dysphonia, hyporeflexia, hypotonia, ptosis.

Disorders of Skin and Appendages:

Infrequent: acne, alopecia, pruritus, erythematous rash, maculopapular rash, dry skin;

Rare: bullous eruption, dermatitis, erythema multiform, abnormal hair texture, hypertrichosis, photosensitivity reaction, follicular rash, skin discoloration, abnormal skin odor, urticaria.

Endocrine Disorders:

Rare: exophthalmos, gynecomastia.

Gastro-Intestinal Disorders:

Infrequent: dysphagia, eructation;

Rare: diverticulitis, fecal incontinence, gastritis, gastroenteritis, glossitis, gum hyperplasia, hemorrhoids, hiccup, gastrointestinal bleeding, melena, hemorrhagic peptic ulcer, proctitis, stomatitis, ulcerative stomatitis, tenesmus, tongue edema, tongue ulceration.

General:

Frequent: allergic reaction, allergy, asthenia; Infrequent: malaise, generalized edema, rigors, weight decrease, weight increase;

Rare: enlarged abdomen, halitosis, otitis media, aphthous stomatitis.

Hematopoietic and Lymphatic:

Infrequent: lymphadenopathy, purpura;

Rare: anemia, anterior chamber eye hemorrhage.

Metabolic and Nutritional Disorders:

Rare: dehydration, hypercholesterolemia, hypoglycemia.

Musculo-Skeletal System Disorders:

Infrequent: arthralgia, arthrosis, dystonia, muscle cramps, muscle weakness;

Rare: hernia.

Psychiatric Disorders:

Infrequent: abnormal dreams, aggressive reaction, amnesia, apathy, delusion, depersonalization, depression, aggravated depression, emotional lability, euphoria, hallucination, neurosis, paranoid reaction, suicide attempt (including suicidal ideation), teeth-grinding, abnormal thinking;

Rare: hysteria, somnambulism, withdrawal reactions.

Reproductive:

Infrequent: dysmenorrhea (2), intermenstrual bleeding (2);

Rare: amenorrhea (2), balanoposthitis (1), breast enlargement (2), female breast pain (2), leukorrhea (2), menorrhagia (2), atrophic vaginitis (2).

(1) - % based on male subjects only: 1005

(2) - % based on female subjects only: 1705

Respiratory System Disorders:

Infrequent: bronchospasm, coughing, dyspnea, epistaxis;

Rare: bradypnea, hyperventilation, sinusitis, stridor.

Special Senses:

Infrequent: abnormal accommodation, conjunctivitis, diplopia, ear ache, eye pain, xerophthalmia;

Rare: abnormal lacrimation, photophobia, visual field defect.

Urinary System Disorders:

Infrequent: dysuria, face edema, nocturia, polyuria, urinary incontinence;

Rare: oliguria, renal pain, urinary retention.

Laboratory Tests:

In man, asymptomatic elevations in serum hepatic transaminases (SGOT [or AST] and SGPT [or ALT]) to a value ≥ 3 times the upper limit of normal have been reported infrequently (approximately 0.6% and 1.1%, respectively) in association with Sertraline hydrochloride administration. The proportion of patients having these elevations was greater in the Sertraline hydrochloride group than in the placebo group. These hepatic enzyme elevations usually occurred within the first 1 to 9 weeks of drug treatment and promptly diminished upon drug discontinuation.

Sertraline hydrochloride therapy was associated with small mean increases in total cholesterol (approximately 3%) and triglycerides (approximately 5%).

Uricosuric Effect

Sertraline hydrochloride capsules are associated with a small mean decrease in serum uric acid (approximately 7%) of no apparent clinical importance.

Other Events Observed During the Postmarketing Evaluation of Sertraline hydrochloride capsules:

Adverse events not listed above which have been reported in temporal association with Sertraline hydrochloride since market introduction include: muscle contractions involuntary, acute renal failure, anaphylactoid reaction, angioedema, blindness, optic neuritis, cataract, increased coagulation times, bradycardia, AV block, atrial arrhythmias, QT-interval prolongation, ventricular tachycardia (including torsade de pointes-type arrhythmias), hypothyroidism, syndrome of inappropriate ADH secretion, agranulocytosis, aplastic anemia, pancytopenia, hematuria, leukopenia, thrombocytopenia, lupus-like syndrome, serum sickness, hyperglycemia, priapism, galactorrhea, hyperprolactinemia, neuroleptic malignant syndrome - like events, extrapyramidal symptoms, oculogyric crisis, serotonin syndrome, psychosis, pulmonary hypertension, severe skin reactions, which potentially can be fatal,

such as Stevens-Johnson Syndrome, epidermal necrolysis, vasculitis, photosensitivity and other severe cutaneous disorders, rare reports of pancreatitis, and liver events.

The causal relationship between Sertraline hydrochloride treatment and the emergence of these events has not been established. The clinical features of hepatic events (which in the majority of cases appeared to be reversible with discontinuation of Sertraline hydrochloride) occurring in one or more patients include: elevated enzymes, increased bilirubin, hepatomegaly, hepatitis, jaundice, abdominal pain, vomiting, liver failure and death. There have been spontaneous reports of symptoms such as dizziness, paresthesia, nausea, headache, anxiety, fatigue, and agitation following the discontinuation of Sertraline hydrochloride treatment.

Adverse reactions following Discontinuation of treatment (or Dose Reduction):
There have been reports of adverse reactions upon the discontinuation of Sertraline hydrochloride (particularly when abrupt), including but not limited to the following: dizziness, abnormal dreams, sensory disturbances (including paresthesias and electric shock sensations), agitation, anxiety, fatigue, confusion, headache, tremor, nausea, vomiting and sweating or other symptoms which may be of clinical significance (See **PRECAUTIONS** and **DOSAGE AND ADMINISTRATION** sections).

Patients should be monitored for these or any other symptoms. A gradual reduction in the dosage over several weeks, rather than abrupt cessation is recommended whenever possible. If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, dose titration should be managed on the basis of the patient's clinical response. These events are generally self-limiting. Symptoms associated with discontinuation have been reported for other selective serotonin reuptake inhibitors (See **PRECAUTIONS** and **DOSAGE AND ADMINISTRATION** sections).

SYMPTOMS AND TREATMENT OF OVERDOSE

On the evidence available, sertraline has a wide margin of safety in overdose.
Of 1,027 cases of overdose involving sertraline hydrochloride worldwide, alone or with other drugs, there were 72 deaths (circa 1999).

Reported overdoses of sertraline alone of up to 13.5 g have been documented. However, an overdose of 2.5 g of sertraline alone had a fatal outcome.

Symptoms:
Symptoms of overdose include serotonin-mediated side effects such as somnolence, gastrointestinal disturbance (such as nausea, vomiting, diarrhea), tachycardia, tremor, agitation and dizziness, ECG changes, anxiety and dilated pupils. Less frequently reported was coma.

Other important adverse events reported with sertraline hydrochloride overdose (single or multiple drugs) include alopecia, decreased libido, ejaculation disorder, fatigue, insomnia, bradycardia, bundle branch block, coma, convulsions, delirium, hallucinations, hypertension, hypotension, manic reaction, pancreatitis, QT-interval prolongation, serotonin syndrome, stupor and syncope.

Treatment:
Establish and maintain an airway, and ensure adequate oxygenation and ventilation, if necessary. Activated charcoal, which may be used with sorbitol, may be as or more effective than lavage, and should be considered in treating overdose. Induction of emesis is not recommended.

Treatment was primar~~il~~y supportive and included monitoring and use of activated charcoal, gastric lavage or cathartics and hydration.

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

Cardiac and vital signs monitoring are recommended along with general symptomatic and supportive measures. There are no specific antidotes for Sertraline hydrochloride.

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

In managing overdosage, the possibility of multiple drug involvement must be considered.

DOSAGE AND ADMINISTRATION

ratio-SERTRALINE (sertraline hydrochloride) is not indicated for use in children under 18 years of age (see WARNINGS: POTENTIAL ASSOCIATION WITH BEHAVIORAL AND EMOTIONAL CHANGES, INCLUDING SELF-HARM).

GENERAL

Sertraline hydrochloride should be administered with food once daily preferably with the evening meal, or, if administration in the morning is desired, with breakfast.

INITIAL TREATMENT

Depression and Obsessive-Compulsive Disorder:

As no clear dose-response relationship has been demonstrated over a range of, 50-200 mg/day, a dose of 50 mg/day is recommended as the initial dose.

Panic Disorder:

Sertraline hydrochloride treatment should be initiated with a dose of 25 mg once daily. After one week, the dose should be increased to 50 mg once daily depending on tolerability and clinical response. No clear dose-response relationship has been demonstrated over a range of 50-200 mg/day.

TITRATION:

In depression, OCD and panic disorder, a gradual increase in dosage may be considered if no clinical improvement is observed. Based on pharmacokinetic parameters, steady-state sertraline plasma levels are achieved after approximately 1 week of once daily dosing; accordingly, dose changes, if necessary, should be made at intervals of at least one week. Doses should not exceed a maximum of 200 mg/day.

The full therapeutic response may be delayed until 4 weeks of treatment or longer. Increasing the dosage rapidly does not normally shorten this latent period and may increase the incidence of side effects.

MAINTENANCE:

During long-term therapy for any indication, the dosage should be maintained at the lowest effective dose and patients should be periodically reassessed to determine the need for continued treatment.

HEPATIC IMPAIRMENT:

As with many other medications, Sertraline hydrochloride should be used with caution in patients with hepatic impairment (See PRECAUTIONS section).

CHILDREN:

(see **WARNINGS: POTENTIAL ASSOCIATION WITH BEHAVIOURAL AND EMOTIONAL CHANGES, INCLUDING SELF-HARM**)

TREATMENT OF PREGNANT WOMEN DURING THE THIRD TRIMESTER:

Post-marketing reports indicate that some neonates exposed to sertraline, SSRIs, or other newer antidepressants late in the third trimester have developed complications requiring prolonged hospitalization, respiratory support, and tube feeding (see PRECAUTIONS section). When treating a pregnant woman with sertraline during the third trimester, the physician should carefully consider the potential risks and benefits of treatment. The physician may consider tapering sertraline in the third

trimester.

SWITCHING PATIENTS TO OR FROM A MONOAMINE OXIDASE INHIBITOR:

At least 14 days should elapse between discontinuation of an MAOI and initiation of therapy with Sertraline. In addition, at least 14 days should be allowed after stopping Sertraline before starting an MAOI (see **CONTRAINDICATIONS** section).

DISCONTINUATION OF SERTRALINE TREATMENT:

Symptoms associated with the discontinuation or dosage reduction of Sertraline hydrochloride have been reported. Patients should be monitored for these and other symptoms when discontinuing treatment or during dosage reduction (See **PRECAUTIONS and ADVERSE REACTIONS** sections).

A gradual reduction in the dose over several weeks rather than abrupt cessation is recommended whenever possible. If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, dose titration should be managed on the basis of the patient's clinical response**. (**see **PRECAUTIONS** and **ADVERSE REACTIONS** sections).

PHARMACEUTICAL INFORMATION

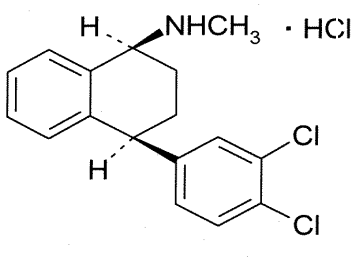
Drug Substance

Generic Name: Sertraline hydrochloride

Chemical Name: (1S, *cis*) -4-(3,4-dichlorophenyl) -1,2,3,4-tetrahydro-N-methyl-l-naphthalenamine hydrochloride

Chemical Name: (1S,cis)-4-(3,4-Dichlorophenyl)-1,2,3,4- tetrahydro-N-methyl-1-napthylamine hydrochloride

Structural Formula:



Molecular Formula: $C_{17}H_{17}NCl_2 \cdot HCl$

Molecular Weight: 342.7

Description: Sertraline hydrochloride is a white to off-white crystalline powder that is slightly soluble in water and isopropyl alcohol, very slightly soluble in 0.1N aqueous hydrochloric acid, practically insoluble in 0.1N aqueous sodium hydroxide, sparingly soluble in ethanol, and soluble in chloroform.

Composition: Capsules are formulated to contain sertraline hydrochloride equivalent to 25, 50 and 100 mg of sertraline and the following non-medicinal ingredients:

Corn starch, Lactose, Magnesium Stearate and Sodium Lauryl Sulfate. In addition the capsule shells contain gelatin and titanium dioxide and

may contain D&C Yellow #10, FD&C Yellow #6 and FD&C Red #40.

Stability and Storage Recommendations:

Sertraline hydrochloride capsules are packaged in white high density polyethylene bottles and are stored at controlled room temperature (between 15^{o} and 30^{o}C).

INFORMATION THE CONSUMER

Information for the Patient:

Please read this information before you start to take your medicine, even if you have taken this drug before.

What you should know about ratio-SERTRALINE:

ratio-SERTRALINE (sertraline hydrochloride) belongs to a family of medicines called SSRIs; Selective Serotonin Reuptake Inhibitors.

ratio-SERTRALINE has been prescribed to you by your doctor to relieve your symptoms of depression, panic disorder or obsessive-compulsive disorder. **Treatment with these types of medications is most safe and effective when you and your doctor have good communication about how you are feeling.**

What you should tell your doctor before taking ratio-SERTRALINE:

All your medical conditions, including a history of seizures, liver or kidney disease;

Any medications (prescription or nonprescription) which you are taking especially monoamine oxidase inhibitor antidepressants, (e.g. phenelzine sulfate, tranylcypromine sulfate or moclobemide) or any other antidepressants, pimozide (an antipsychotic drug), drugs used to treat diabetes, drugs used to thin the blood (anticoagulants) or drugs containing tryptophan;

If you are pregnant or thinking about becoming pregnant, or if you are breast-feeding; Your habits concerning alcohol consumption. Any natural or herbal products you are taking (e.g. St. John's Wort).

How to take ratio-SERTRALINE:

It is very important for you to take **ratio-SERTRALINE** exactly as your doctor has instructed. The usual starting dose is 50 mg of **ratio-SERTRALINE**/day for depression and obsessive-compulsive disorder. If you are taking **ratio-SERTRALINE** for panic disorder, your doctor may start you at 25 mg/day.

Your doctor may decide to increase the dose up to 200 mg/day.

Never increase or decrease the amount of **ratio-SERTRALINE** you, or those in your care if you are a caregiver or guardian, are taking unless your doctor tells you to and do not stop taking this medication without consulting your doctor (See under **Precautions when taking ratio-SERTRALINE**).

You should continue to take your medicine even if you do not feel better, as it may take approximately four weeks for your medicine to work.

ratio-SERTRALINE should be taken with food; either in the morning or evening. You should swallow the capsule whole; do not chew it.

Keep taking **ratio-SERTRALINE** until your doctor tells you to stop. Your doctor may tell you to continue to take your medicine for several months. Continue to follow your doctor's instructions.

If you miss taking a dose of **ratio-SERTRALINE**, do not worry, just take the next dose when you normally do. Do not take 2 doses at once. It is important to discuss with your doctor what you should do if you miss several doses of **ratio-SERTRALINE**.

You should avoid taking St. John's Wort if you are taking **ratio-SERTRALINE**.

When not to use ratio-SERTRALINE:

Do not use **ratio-SERTRALINE** if you are allergic to it or to any of the components of its formulation (see list of components at the end of this section). Stop taking the drug and contact your doctor immediately if you experience an allergic reaction or any severe or unusual side effect.

Precautions when taking ratio-SERTRALINE:

You may experience some side effects such as nausea, headache, dry mouth, diarrhea, sleep disturbance and loss of appetite. Other effects may include drowsiness, sexual problems, nervousness and tremor. Consult your doctor if you experience these or other side effects, as the dose may have to be adjusted.

Particularly in the first few weeks or when doses are adjusted, a small number of patients taking drugs of this type may feel worse instead of better; for example, they may experience unusual feelings of agitation, hostility or anxiety, or have impulsive or disturbing thoughts such as thoughts of self-harm or harm to others. Should this happen to you, or to those in your care if you are a caregiver or guardian, consult your doctor immediately; do not discontinue your medication on your own.

ratio-SERTRALINE does not usually affect people's normal activities. However, some people feel sleepy while taking it, in which case they should not drive or operate machinery.

Avoid alcoholic drinks while taking **ratio-SERTRALINE**.

Contact your physician before stopping or reducing your dosage of **ratio-SERTRALINE**. Symptoms such as dizziness, abnormal dreams, electric shock sensations, agitation, anxiety, difficulty concentrating, headache, tremor, nausea, vomiting, sweating or other symptoms may occur after stopping or reducing the dosage of ratio-SERTRALINE. Such symptoms may also occur if a dose is missed. These symptoms usually disappear without needing treatment. Tell your doctor immediately if you have these or any other symptoms. Your doctor may adjust the dosage of **ratio-SERTRALINE** to alleviate the symptoms.

Post-marketing reports indicate that some newborns whose mother took an SSRI (Selective Serotonin Reuptake Inhibitors), or other newer antidepressants, such ratio-SERTRALINE, during pregnancy have developed complications at birth requiring prolonged hospitalization, breathing support, and tube feeding. Reported symptoms include: feeding and/or breathing difficulties, seizures, tense or overly relaxed muscles, jitteriness and constant crying. In most cases, the newer antidepressant was taken during the third trimester of pregnancy. These symptoms are consistent with either a direct adverse effect of the antidepressant on the baby, or possibly a discontinuation syndrome caused by sudden withdrawal from the drug. These symptoms normally resolve over time. However, if your baby experiences any of these symptoms, contact your doctor as soon as you can. If you are pregnant and taking an SSRI, or other newer antidepressant, you should discuss the risks and benefits of the various treatment options with your doctor. It is very important that you do NOT stop taking these medications without first consulting your doctor.

What to do in case of overdose:

If you have taken a large number of capsules all at once, contact either your doctor, hospital emergency department or nearest poison control center immediately, even though you may not feel sick.

How to store ratio-SERTRALINE:

Store at room temperature (15^{o} to 30^{o}C) in a dry place.
Keep the container tightly closed.
Keep out of reach of children.

If your doctor decides to stop **ratio-SERTRALINE** treatment, return any leftover medicine to your pharmacist to safely dispose of it. Keep it only if your doctor tells you to do so.

What ratio-SERTRALINE contains:

ratio-SERTRALINE is available as 25 mg (yellow capsule), 50 mg (white and yellow capsule) and 100 mg (orange capsule). Sertraline hydrochloride is the active ingredient. Nonmedicinal ingredients

include: cornstarch; lactose (anhydrous); magnesium stearate; sodium lauryl sulfate. Capsule shells contain gelatine, titanium dioxide and dye D&C Yellow #10. In addition, capsules 25 and 50 mg also contain dye FD&C Yellow #6 and capsules 100 mg also contain dye FD&C Red #40.

Who manufactures ratio-SERTRALINE:
ratio-SERTRALINE capsules are manufactured by ratiopharm inc.

Reminder: This medicine has been prescribed only for you. Do not give it to anybody else. If you have any further questions, please ask your doctor or pharmacist.

AVAILABILITY OF DOSAGE FORMS

The capsules are available as follows:

25 mg capsules: Hard gelatine capsules filled with white to off-white powder. "Ratio-Sertraline 25" printed in black ink on yellow opaque cap and "rph 297 A" printed in black ink on yellow opaque body, supplied in white high density polyethylene bottles of 100 capsules.

50 mg capsules: Hard gelatine capsules filled with white to off-white powder. "Ratio-Sertraline 50" printed in black ink on yellow opaque cap and "rph 297 B" printed in black ink on white opaque body, supplied in white high density polyethylene bottles of 100 and 250 capsules.

100 mg capsules: Hard gelatine capsules filled with white to off-white powder. "Ratio-Sertraline 100" printed in black ink on orange opaque cap and "rph 297 C" printed in black ink on orange opaque body, supplied in white high density polyethylene bottles of 100 and 250 capsules.

PHARMACOLOGY

Animal Pharmacology:

Sertraline is a highly selective and potent inhibitor of neuronal 5HT uptake, both *in vitro* and *in vivo*. Sertraline is highly active in several behavioral and biochemical models in which clinically effective antidepressants are also active. Sertraline has no significant effects on cardiac function and only transient effects on pulmonary function are seen with high intravenous doses. A transient reduction in K+ excretion was observed in conscious dogs, which dissipated after the second daily dose of 4 mg/kg po. Sertraline increases gastric acid secretion in rats but does not induce any pathological changes in the stomachs of dogs, even after several months of treatment. Sertraline is a mild inducer of hepatic microsomal cytochrome P450.

Rats receiving a 32 mg/kg oral dose of sertraline (5 to 10 fold the therapeutic dose in man) in combination with lithium (200 mg/kg) had increased plasma levels of lithium compared to saline-treated controls.

Characterization in animal test systems produced evidence that sertraline shares pharmacologic properties common to clinically effective antidepressant agents and lacks cardiovascular or anticholinergic effects.

Preclinical Pharmacokinetics

Data from the pharmacokinetic studies in the mouse, rat and dog are contained in **TABLE 3**. The elimination half-life of sertraline was 2.5 hours in the mouse and about 5 hours in the rat and dog. The plasma clearance of sertraline was estimated at 59 and 49 mL/min/kg in the rat and dog, respectively (**TABLE 3**). Plasma clearance represents metabolic clearance in rat and dog, since sertraline is not excreted unchanged in urine or bile. The oral bioavailability of sertraline was 70, 36 and 22% in the mouse, rat and dog, respectively (**TABLE 3**).

In bile duct-cannulated rats and dogs receiving [1-^{14}C] sertraline by oral gavage, 62 to 94% of the

dose was absorbed. Therefore, sertraline undergoes first-pass metabolism with oral absorption.

The primary amine metabolite (desmethylsertraline), was present in the circulation of all species studied. This metabolite has no pharmacologic activity *in vivo*. Its elimination half-life is 2-3 times longer than that of sertraline in all species studied.

The plasma protein binding of sertraline in rat, dog and man was 97.2, 98.9 and 98.6%, respectively, at 100 ng/mL plasma concentrations.

Sertraline distributes extensively into tissues. The volume of distribution of sertraline in rat or dog was 23 or 25 l/kg (**TABLE 3**).

Enzyme induction activity: Following a five day treatment in rats, 80 mg/kg/day of sertraline (oral dose) was approximately equivalent to 50 mg/kg/day of phenobarbital in inducing the *in vitro* O-demethylation of p-chloroanisole. Following a three week treatment of 90 mg/kg/day in dogs, the half-life of antipyrine decreased from a pre-treatment value of 54 minutes to 30 minutes.

Rat, dog and man form the primary amine metabolite (desmethylsertraline) by the N-demethylation of sertraline; form ketone by the oxidative deamination of sertraline and primary amine. Alpha -hydroxy ketone glucuronides diastereomeric pair are excreted as end products of this metabolic pathway. In man, the ∝-hydroxy ketone glucuronide diastereomers were the major but not the sole end product of the deamination pathway, as both the ketone and ∝-hydroxy ketone metabolites underwent reduction to some extent. -Conjugates of the corresponding reductive metabolites, the alcohol and dihydroxy metabolite, were excreted in urine. Although not identified in excreta of rat or dog, the alcohol and dihydroxy metabolites were formed *in vitro* by incubation of ketone in hepatic microsomes from both species. Sertraline can alternatively be converted to N-hydroxy sertraline glucuronide or sertraline carbamoyl-0-glucuronide.

Sertraline carbamoyl-0-glucuronide was the major excretory metabolite in the dog and also was formed by rat and man. N-hydroxy sertraline glucuronide was identified only in rat and dog. There

was a greater excretion of metabolites in bile by the rat and dog than by man.

TABLE 3

Summary of Pharmacokinetics for Sertraline and the Primary Amine Metabolite in the Mouse, Rat, Dog and Man.

		Sertraline*						**Primary Amine***		
Species	Sertraline dose (mg/kg) and Route of Administration	$t_{½}$ (hr)	V_D (l/kg)	C1 (mL/min/kg)	% Oral Bioavail	Cmax (μg/mL)	AUC (mg hr/l)	$t_{½}$ (hr)	Cmax (μg/mL)	AUC (mg/hr/l)
Mouse	29 (SC and PO)	2.5	--	--	70	0.31	1.6	7.4	0.41	5.3
Rat	5 (IV and PO)	4.5	23	59	36	0.062	0.51	14	0.051	0.71
Rat	25 (IP and PO)	6.5	--	--	--	0.31	4.5	10.5a	0.11	1.8
Dog	5 (IV) and 10 (PO)	5.2	25	49	22	0.15	1.4	7.1[a]	0.16	4.6
Dog[b]	10 (PO)	--	--	--	--	0.32	2.3	--	0.21	3.0
Dog[b]	30 (PO)	--	--	--	--	0.93	8.6	--	0.49	7.8
Dog[b]	90 (PO)	--	--	--	--	3.1	33.6	--	1.8	29.5
Man[c]	3 PO	26	--	--	--	0.19	2.8	65	0.14	2.3

- *: $T_{1/2}$, V_D and C1 in mouse, rat and dog were based on data from parenteral route of sertraline hydrochloride administration, while Cmax and AUC were based on data following oral administration.
- a: Based on parenteral administration of primary amine metabolite.
- b: Steady-state values (average of days 3 and 36) of toxicology study # 82-375-08.
- c: Sertraline $t_{½}$ based on data at doses of 50 to 400 mg/day. Cmax and AUC for drug and metabolite were steady-state values (day 14) of 200 mg dose subjects.

TOXICOLOGY

Acute Toxicity: mice and rats

ACUTE ORAL AND INTRAPERITONEAL TOXICITY STUDIES IN MICE AND RATS

Species	Sex	LD_{50} (mg Sertraline base /kg)		Max Mortality (hr)	
		Oral	**IP**	**Oral**	**IP**
Mice	M	548 (495-612)	73 (66-79)	2 ¼	1
	F	419 (371-465)		1 3/4	
Rats	M	1591 (1348-1847)	79 (70-90)	24	24
	F	1327 (1071-1562)		4.5	

Signs of toxicity observed in both mice and rats dosed orally and by intraperitoneal administration included hyperactivity, convulsions, depression, weakness, decreased food consumption, and weight gain inhibition. Oral administration in both mice and rats produced exophthalmia, soft stools, and laboured respiration. Orally dosed rats also showed marked salivation. Acute oral administration produced no gross pathological findings. Acute intraperitoneal administration, on the other hand, caused adhesion of the intestines or pancreas to the liver in 2 of 10 male mice and liver lobe adhesions which were dose-related in rats.

Sertraline was also given in single doses of 10, 20, 30, and 50 mg base/kg p.o. (in capsules) to two female beagle dogs at each dose. At the lowest level, dogs were mydriatic and anorectic but otherwise asymptomatic. At higher doses, increased salivation, tremors and twitches were observed, along with the mydriasis and anorexia. None of the dogs at any dose level exhibited motor stimulation, circling or stereotypy. The duration of the anorexia was 12 to 15 hr., but eating resumed late in the day after treatment and the dogs recovered uneventfully.

Chronic Toxicity/Oncogenicity

<table>
<tr><th>SPECIES</th><th>ROUTE</th><th>DOSE mg/kg/day</th><th>ANIMAL PER DOSE LEVEL</th><th>DURATION</th><th>FINDINGS</th></tr>
<tr><td colspan="6">36 Day Diet Study in Mice</td></tr>
<tr><td>CD-1 Mice</td><td>Diet</td><td>0
10
40
80</td><td>10/sex</td><td>36 Days</td><td>
Drug and desmethyl metabolite serum levels drug related:
<table>
<tr><td></td><td colspan="2">Serum Concentration (ng/mL)</td><td colspan="2"></td></tr>
<tr><td></td><td colspan="2">Drug</td><td colspan="2">Metabolite</td></tr>
<tr><td>Dose (mg/kg/day)</td><td>Male</td><td>Female</td><td>Male</td><td>Female</td></tr>
<tr><td>22</td><td>17</td><td>40</td><td>23</td></tr>
<tr><td>10</td><td>52</td><td>16</td><td>181</td><td><10</td></tr>
<tr><td>40</td><td>142</td><td>63</td><td>307</td><td>169</td></tr>
<tr><td>80</td><td></td><td></td><td></td><td></td></tr>
</table>
Some degree of alopecia occurred in three mid-dose animals and one high-dose animal. Fatty change occurred in the livers of 8/10 high-dose males compared to 3/10 control males. On the basis of these findings, daily doses of 10, 20 and 40 mg Sertraline hydrochloride base/kg were proposed for the 2-year feeding study.
</td></tr>
<tr><td colspan="6">2 Year Diet Study in Mice</td></tr>
<tr><td>CD-1 Mice</td><td>Diet</td><td>0
0
10
20
40</td><td>50/Sex</td><td>24 Months</td><td>Survival of drug treated females was slightly less than control. Bronchioalveolar adenomas occurred in 9/49, 1/50, and 12/50 low-, mid-, and high dose females compared to 6/50 and 2/50 in females of the two control groups. Hepatocellular adenomas were observed in 8/50, 8/50 and 12/50 low-, mid-, and high dose males compared to 3/50 and 4/50 males in the two control groups. These tumors were benign and the type usually occurring spontaneously in this strain of mouse. There were no treatmentrelated increases in tissue specific or total malignant tumors.</td></tr>
<tr><td colspan="6">16 Day P.O. Study in Rats</td></tr>
<tr><td>Sprague Dawley Rats</td><td>Gavage</td><td>0
40
80
160</td><td>5/sex</td><td>16 Days</td><td>Anorexia and transient body weight gain inhibition; latter effect was high in high-dose females. Dose-related increase in liver weights due to microsomal enzyme induction; centrilobular degeneration at all dose levels and slightly elevated SGPT and SGOT at 160 mg/kg only.</td></tr>
<tr><td colspan="6">6 Week Diet Study in Rats</td></tr>
<tr><td>Sprague Dawley Rats</td><td>Diet</td><td>0
10
40
80</td><td>10/sex</td><td>6 Weeks</td><td>Minimal effect on body weight gain of males and slight inhibition of body weight (<10%) in mid- and high dose females. Liver weight increase in mid- and high dose males and females; hepatocellular hypertrophy and minimal midzonal fatty change in high-dose males and females and mid-dose males accompanied by slight elevations in serum SDH, GOT and 5'NT in some animals.
No adverse effect level: 10 mg/kg/day.</td></tr>
<tr><td colspan="6">3 Month P.O. Study in Rats</td></tr>
<tr><td>Sprague Dawley Rats</td><td>Gavage</td><td>0
10
40
80</td><td>15M
10F</td><td>3 Months</td><td>Dose related plasma levels at 10 and 40 mg/kg.
<table>
<tr><td colspan="6">Plasma Levels (µg/mL) of Drug 2 h Post-Dose on Days 1, 5 and 30</td></tr>
<tr><td>Dose (mg/kg/day)</td><td>Sex</td><td></td><td>Day 1</td><td>Day 5</td><td>Day 30</td></tr>
<tr><td>80</td><td>M</td><td>Mean
+ SD</td><td>0.63
0.19</td><td>0.31
0.05</td><td>0.46
0.20</td></tr>
</table>
</td></tr>
</table>

<table>
<tr><th>SPECIES</th><th>ROUTE</th><th>DOSE mg/kg/day</th><th>ANIMAL PER DOSE LEVEL</th><th>DURATION</th><th>FINDINGS</th></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td>
<table>
<tr><td></td><td>F</td><td>Mean</td><td>0.75</td><td>0.37</td><td>0.84</td></tr>
<tr><td></td><td></td><td>+ SD</td><td>0.19</td><td>0.10</td><td>0.48</td></tr>
<tr><td>40</td><td>M</td><td>Mean</td><td>0.70</td><td>0.20</td><td>0.32</td></tr>
<tr><td></td><td></td><td>+ SD</td><td>0.11</td><td>0.06</td><td>0.18</td></tr>
<tr><td></td><td>F</td><td>Mean</td><td>0.42</td><td>0.33</td><td>0.92</td></tr>
<tr><td></td><td></td><td>+ SD</td><td>0.14</td><td>0.05</td><td>0.28</td></tr>
<tr><td>10</td><td>M</td><td>Mean</td><td>0.25</td><td>0.10</td><td>0.10</td></tr>
<tr><td></td><td></td><td>+ SD</td><td>0.10</td><td>0.03</td><td>0.03</td></tr>
<tr><td></td><td>F</td><td>Mean</td><td>0.19</td><td>0.14</td><td>0.27</td></tr>
<tr><td></td><td></td><td>+ SD</td><td>0.06</td><td>0.03</td><td>0.08</td></tr>
</table>
Dose related increases in absolute and relative liver weights due to induction of microsomal enzymes; increases associated with centrilobular hepatocellular hypertrophy; mild midzonal fatty changes observed in 10/15 males and 1/10 females at 80 mg/kg.
</td></tr>
<tr><td colspan="6">2 Year Diet Study in Rats</td></tr>
<tr><td>Long Evans Rats</td><td>Diet</td><td>0
10
20
40</td><td>65/sex</td><td>24 Months</td><td>Interim sacrifice (15/sex) at 6 months: Kidney/body weight was increased. Increase in mean absolute and relative liver weights in males and females at high dose and in females at mid-dose.
2 years sacrifice: Deaths were dose-related; inhibition of weight gain was dose-related in males and present at high dose only in females. Slight elevations of serum 5'nucleotidase (5'NT) activity in the high and mid-dose groups occurred throughout the study.

Increase of liver and kidney/body weight ratios. These effects are considered to be related to drug-metabolizing enzyme induction. Hepatocytes with large clear fat-containing vacuoles were observed; number of affected animals in groups was dose related in females but distribution was more erratic in males. In no case was there evidence of necrosis or of an inflammatory response. There were no treatment related effects on the number of tumor bearing animals, total malignant tumors or total benign tumors in either sex. Hence, there was no evidence of oncogenic potential.</td></tr>
<tr><td colspan="6">Rat (Special Toxicology Study) I.V.</td></tr>
<tr><td>Sprague Dawley Rats</td><td>I.V.</td><td>0
0.125
0.250
0.500</td><td>10/sex</td><td>15 days
16 days
17 days
18 days</td><td>Hemoglobinuria, identifiable only by reagent test strip as early as 5 minutes after injection, the only treatment related clinical pathology finding, was not dose-related. It is analogous to the in vitro hemolytic effects of Sertraline hydrochloride in the concentrations utilized in this study, i.e., 0.125, 0.25, and 0.5 mg/mL. No hemolysis was detected in vitro when red cells were exposed to 0.005 mg/mL Sertraline hydrochloride. In vitro studies have also demonstrated incompatibility (cloudiness) of plasma exposed to equal volumes of 0.25 and 0.5 mg Sertraline hydrochloride/mL. These data suggest that intravenous Sertraline hydrochloride solutions should be administered by drip rather than by bolus injections. A total of 3 high-dose and 12 control rats had perivascular hemorrhage and/or chronic perivasculitis at the injection site in the tail.</td></tr>
<tr><td colspan="6">7 Day Oral Study in Dogs</td></tr>
<tr><td>Beagle</td><td>Oral (Capsule)</td><td>0
15
45</td><td>2 Males</td><td>7 Days</td><td>Slight anorexia, body weight loss and hind limb weakness at high dose. Plasma drug levels suggested good oral absorption.
<table>
<tr><td colspan="4">Plasma Concentrations of Drug 3 h Post Dose on Days 1 and 7</td></tr>
<tr><td colspan="2"></td><td colspan="2">Plasma Concentration (µg/mL)</td></tr>
<tr><td>Dose (mg/kg/day)</td><td>Dog No.</td><td>Day 1</td><td>Day 7</td></tr>
</table>
</td></tr>
</table>

SPECIES	ROUTE	DOSE mg/kg/day	ANIMAL PER DOSE LEVEL	DURATION	FINDINGS
					<table><tr><td></td><td></td><td></td><td></td></tr><tr><td>45</td><td>832255 832259</td><td>2.28 2.04</td><td>2.48 0.82</td></tr><tr><td>15</td><td>832258 832260</td><td>1.12 0.42</td><td>0.13 0.68</td></tr></table> Apparent losses of small lymphocytes from thymus was observed; lymphoid depletion in spleen, mesenteric lymph nodes and ileum were seen in one high dose dog.
14 Day Oral Study in Dogs					
Beagle	Oral (Capsule)	0 40 80 160	1/sex	14 Days	Dose related anorexia and body weight loss. Increase of serum alkaline phosphatase at high dose and of SGPT in the high dose females. Depletion of small lymphocytes from spleen in the 80 mg male and from spleen and ileum in the high dose male.
3 Month Oral Study in Dogs					
Beagle	Oral (Capsule)	0 10 40 80	3/sex	3 Months	Dose-related CNS stimulation during the first one or two weeks of treatment. One high-dose animal died of convulsions 5.5 hours after drug administration on the first day of treatment. Necropsy of this animal revealed generalized congestion and lymphoid depletion of the thymus, spleen and mesenteric lymph node consistent with the cause of death. Elevated alkaline phosphatase (ALP) values were measured in all dogs of the high-dose group and in 2 males and 2 females of the mid-dose group. The ALP elevation together with a trend toward increased liver weights reflect the ability of Sertraline hydrochloride to induce drug metabolizing enzymes at 40 and 80 mg/kg. Slight SGPT elevations in the high-dose animals were not associated with histopathological changes.
6 Month Oral Study in Dogs					
Beagle	Oral (Capsule)	0 10 30 90	4/sex	6 Months	Pronounced clinical signs of CNS stimulation were observed at high dose; they diminished in intensity or completely disappeared after 1 to 2 weeks of dosing. At the 90 mg/kg dose level increase in absolute and relative liver weights, proliferation of smooth endoplasmic reticulum and mild serum alkaline phosphatase elevations were all consistent with Sertraline hydrochloride being an enzyme inducer. This was demonstrated by a shortening of the plasma half-life of antipyrine at the high-dose level only (30 min compared to 54 min). A few dogs at 30 mg/kg had slight sporadic alkaline phosphatase elevations. Some dogs at the high-dose level only had SGPT elevations. The mild bile duct hyperplasia detected in two highdose males could have been drug-related; however, this lesion sometimes is observed in control beagle dogs.
1 Year Oral Study in Dogs					
Beagle	Oral (Capsule)	0 10 30 90	4/sex	1 year	Dose-related incidences of central and autonomic nervous system clinical signs during the first few weeks of the study were observed. Slight to moderate elevations in serum alkaline phosphatase activity occurred in 1/8, 4/8 and 7/8 low-, mid- and high-dose dogs, respectively. SGPT levels were increased in 2/8 high-dose animals. Liver/body weight ratios were increased in high-dose males (25%)

<table>
<tr><th>SPECIES</th><th>ROUTE</th><th>DOSE mg/kg/day</th><th>ANIMAL PER DOSE LEVEL</th><th>DURATION</th><th>FINDINGS</th></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td>and females (32%) and in mid-dose females (25%). Sertraline hydrochloride was previously shown to be an inducer of hepatic microsomal drug metabolizing enzymes, a phenomenon often associated with elevated liver weights and serum alkaline phosphatase activity in dogs. There were no gross or microscopic histologic changes in the liver or in other tissues. Plasma levels of Sertraline hydrochloride and its desmethyl metabolite, CP- 62,508, confirmed dose-related systemic exposure throughout the study
<table>
<tr><td colspan="8">CMAX OF DRUG AND 0-24 HOUR AUC OF METABOLITE</td></tr>
<tr><td colspan="2">(mg/kg)</td><td colspan="3">Cmax CP-51,974 (µg/mL)</td><td colspan="3">AUC CP-62,508 (mg.hr/l)</td></tr>
<tr><td></td><td></td><td>DAY 1</td><td>DAY 99</td><td>DAY 274</td><td>DAY 1</td><td>DAY 99</td><td>DAY 274</td></tr>
<tr><td>10</td><td>MEAN
S.D.</td><td>0.344
0.165</td><td>0.218
0.142</td><td>0.262
0.190</td><td>3.4
1.7</td><td>2.6
0.8</td><td>3.0
1.0</td></tr>
<tr><td>30</td><td>MEAN
S.D.</td><td>0.723
0.454</td><td>0.643
0.299</td><td>1.26
0.90</td><td>4.9
2.3</td><td>8.8
4.4</td><td>11.6
5.0</td></tr>
<tr><td>90</td><td>MEAN
S.D.</td><td>1.33
0.81</td><td>1.06
0.61</td><td>2.16
1.24</td><td>11.8
6.2</td><td>12.2
5.0</td><td>39.9
25.1</td></tr>
</table>
</td></tr>
<tr><td colspan="6">A Study of the Reproduction and Fertility of Rats. Segment I (Extended to produce F2 litters)</td></tr>
<tr><td>Rat</td><td>Oral (gavage)</td><td>0
10
40
80</td><td>F0=30F/dose
F0=15M/dose</td><td></td><td>F0 males were treated in the 64 days prior to mating and throughout mating. F0 females were treated in the 14 days prior to mating and during mating and gestation. Offspring (F1 generation) were raised for 3 months free of drug treatment and then mated to produce an F2 generation which, together with F1 dams were sacrificed 21-24 days post-partum. The F0 treated dams showed decreased pregnancy rates, most marked at 80 mg/kg. The pregnancy rates were 47%, 83%, 92% and 100 % respectively in the high, mid, low dose and control groups. Survival of F1 pups to Day 4 post-partum was also depressed in a dose-related order. High-dose F1 pups showed evidence of earlier behavioral development</td></tr>
<tr><td colspan="6">Foetotoxicity and Fertility Study (FDA Protocol, Segment I) in Rats by Oral Administration</td></tr>
<tr><td>Rat</td><td>Oral (gavage)</td><td>10
20
80</td><td>20M
40F</td><td></td><td>Males were treated for 71 days before mating. Females were treated for 2 weeks before mating, during mating and throughout gestation. Four additional groups of 20 undosed females were mated with the same males to test their fertility. Drug treatment produced inhibition (approximately 20 g) during pregnancy in all treated females and reduced birth weights of pups at Day 1 postpartum (males: # 0.15 g, females: # 0.3 g). At Days 4 and 21 of age, the weights of the pups treated also led to a lower neonatal survival rate at the two highest doses (survival was 61% and 69% respectively at high- and mid-dose groups compared with a survival of 94% in the low-dose group and 98% in controls at 21 days). Some of this mortality was attributed to a higher incidence of hemoperitoneum in 18 high dose and 12 mid-dose than in 6 low dose and 1 control F1 neonates. Hemoperitoneum was not seen in newborn pups in any of the other studies. In behavioral tests, some early hyperactivity observed in pups of the treated groups was consistent with the pharmacology of the drug. No adverse effects were observed in the F2 generation.</td></tr>
</table>

SPECIES	ROUTE	DOSE mg/kg/day	ANIMAL PER DOSE LEVEL	DURATION	FINDINGS
Feototoxicity Study (Segment II) in Rat by the Oral Route					
Rat	Oral (gavage)	10 20 80	20F		Drug administered to inseminated females at days 6-15 post-insemination. Treatment caused transient aggressiveness at the beginning of the treatment period and reduced body weight gain (an average of 26 g) of the high-dose dams. A slight delay in ossification of fetuses appears to be related to lower fetal weights in the midand high-dose groups which were probably functions of maternal toxicity (Ex: delay in ossification of metacarpus in 20 pups among 1181 at 80 mg/kg and in 13 pups among 1825 in the control group).
Feototoxicity Study (FDA Segment II) in Rabbits by the Oral Route					
Rabbit	Oral (gavage)	05 20 40	20F		Sertraline hydrochloride administered to pregnant rabbits during organogenesis (days 7 to 18 post insemination). At the highest dose level of 40 mg/kg, the compound induced severe maternal toxicity which in turn delayed the ossification processes of the fetuses (Ex: delay in ossification in hyoid bone: control = 20%, 40 mg/kg = 36%; in Talus bone: control = 27%, 40 mg/kg = 44%).

Peri- Post-Natal Studies

SPECIES	ROUTE	DOSE mg/kg/day	ANIMAL PER DOSE LEVEL	DURATION	FINDINGS
Peri- Post-Natal Study in Rats (Segment III) by the Oral Route					
Rat	Oral	10 20 80	20F		Sertraline hydrochloride was administered by gavage to inseminated rats from day 15 post-insemination until parturition and throughout the whole lactation period. The treatment produced some adverse effects in dams and pups at the two higher dose levels; a dose-related delay in body weight gain of the dams during gestation and lactation in mid- and high-dose groups was observed. In some animals in each of these groups, hyperactivity was observed during the first few days of treatment. Food and water consumption was also affected in these two dose groups. Statistically significant decreases in mean litter size were observed at the high dose level on Day 1 postpartum, at the mid- and high-dose levels on Day 4 postpartum; this effect was dose related on Day 21 postpartum. The mean body weights of pups were lower in both sexes at both of the higher dose level groups when compared to controls on Days 1 post-partum but there were no statistically significant differences between the groups on Day 21 post-partum. No external or visceral anomalies were observed in the pups that died during the lactation phase or were sacrificed at weaning. The postnatal development of pups was also affected by the treatment of dams: fewer pups showed positive responses on the last day when reflexes were tested and the appearance of the incisors was retarded. This was most evident at the high-dose, but also to some extent at the mid-dose. Post-weaning examination revealed no treatment related changes.
Experiment (Segment III) to Further Investigate the Effect of Sertraline on Neonates					
Rat	Oral (gavage)	80			A second Segment III Study was carried out to further investigate the effects of Sertraline hydrochloride on the neonates. In this study, pups from dams treated at 80 mg base/kg were fostered by untreated dams and, vice versa, pups from untreated dams were fostered by drug treated dams. As observed in previous studies, Sertraline hydrochloride affected the weight gain of the dams (body weight difference between control and high dose group: at 20 day of pregnancy = 34 g, at 21 days post-partum = 19 g). The effects observed on the progeny can be separated into two categories:

					Those directly related to the in utero exposure of fetuses: perinatal mortality and pup weight impairment on Day 1; those related to the exposure during lactation: post-natal growth impairment and delay in development. Vision and hearing, evaluated after weaning, were not affected.

Experiment to delineate the prenatal period of fetal vulnerability					
Rat	Oral (gavage)	80	20 20 x 4		Sertraline hydrochloride administered to pregnant rats throughout or during late gestation, has been shown to exert deleterious effects on neonatal growth and survival to Day 4 post-partum. Another experiment was done in which Sertraline hydrochloride (80 mg base/kg/day) was administered in 0.1% methylcellulose by oral gavage to 4 groups of pregnant dams (20/group) from Day 0 to Days 5, 10, or 15 and throughout gestation, respectively, in order to delineate the prenatal period of fetal vulnerability. Pup survival was unaffected by Sertraline hydrochloride treatment during the first 5, 10 or 15 days of gestation. Mortality of live-born pups in these groups during the first 4 days of life ranged from 0.8 % to 3% compared with 2% for the controls whereas 56% of pups born alive to dams treated throughout the gestational period did not survive their first 4 days of life. However, survival of pups from Day 4 to Day 21 (lactation index) was comparable in all treatment and control groups. Pups born to mothers dosed throughout gestation also weighed less than control on Days 1 and 4 post partum, but body weights of pups were comparable to control by Day 14. This experiment demonstrates that the immediate prenatal period, gestation Days 16-21, is the period of vulnerability of the neonatal pup for survival from the in utero effects of a high dose (80 mg/kg) of Sertraline hydrochloride.

Genotoxicity

Genotoxicity studies including Ames Salmonella and mouse lymphoma TK + /TK- assays for point mutations, tests for cytogenetic aberrations *in vivo* on mouse bone marrow and on human lymphocytes *in vitro* with and without metabolic activation were uniformly negative.

Sertraline did not induce mutations at the gene level in the Ames microbial assay with and without metabolic activation against Salmonella typhimurium strains TA 1535, TA 1537, TA 98, and TA 100 nor at the chromosomal level in bone marrow of mice treated with 80 mg/kg p.o. (*in vivo* cytogenetic assay) or in human lymphocytes (*in vitro* cytogenetic assay) at 0.5 to 25 mg/mL in culture. Sertraline produced no significant increase in mutant frequency in L5178Y mouse lymphoma (TK +/-) cells either in the presence or absence of exogenous metabolic activation by normal rat liver S9 microsomes.

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