Freedep®

(Sertraline HCl USP)

فری ڈیپ

COMPOSITION:

FREEDEP 50mg:
Each film coated tablet contains:
Sertraline....50mg
as Sertraline HCL USP.
(USP Specs.)

FREEDEP 100mg:
Each film coated tablet contains:
Sertraline....100mg
as Sertraline HCL USP.
(USP Specs.)

DESCRIPTION

Freedep (Sertraline HCl) is a selective serotonin reuptake inhibitor (SSRI) for oral administration. It is chemically unrelated to other SSRIs, tricyclic, tetracyclic, or other available antidepressant agents.

CLINICAL PHARMACOLOGY

Pharmacodynamics

The mechanism of action of sertraline is presumed to be linked to its inhibition of CNS neuronal uptake of serotonin (5HT). Studies at clinically relevant doses in man have demonstrated that sertraline blocks the uptake of serotonin into human platelets. In vitro studies in animals also suggest that sertraline is a potent and selective inhibitor of neuronal serotonin reuptake and has only very weak effects on norepinephrine and dopamine neuronal reuptake. In vitro studies have shown that sertraline has no significant affinity for adrenergic (alpha1, alpha2, beta), cholinergic, GABA, dopaminergic, histaminergic, serotonergic ($5HT_{1A}$, $5HT_{1B}$, $5HT_2$), or benzodiazepine receptors; antagonism of such receptors has been hypothesized to be associated with various anticholinergic, sedative, and cardiovascular effects for other psychotropic drugs. Sertraline does not inhibit monoamine oxidase.

Pharmacokinetics

Systemic Bioavailability: In man, following oral once-daily dosing over the range of 50 to 200 mg for 14 days, mean peak plasma concentrations (C_{max}) of sertraline occurred between 4.5 to 8.4 hours post-dosing. The average terminal elimination half-life of plasma sertraline is about 26 hours. Based on this pharmacokinetic parameter, steady-state sertraline plasma levels should be achieved after approximately one week of once-daily dosing.

AUC was slightly increased when drug was administered with food but the C_{max} was 25% greater, while the time to reach peak plasma concentration decreased from 8 hours post-dosing to 5.5 hours.

Metabolism: Sertraline undergoes extensive first pass metabolism. Unchanged sertraline was not detectable in the urine. For the same period, about 40-45% of the administered radioactivity was accounted for in feces, including 12-14% unchanged sertraline.

Protein Binding: In vitro protein binding studies performed with radiolabeled ^{3}H-sertraline showed that sertraline is highly bound to serum proteins (98%) in the range of 20 to 500 ng/ml.

Age: Sertraline plasma clearance in a group of 16 (8 male, 8 female) elderly patients treated for 14 days at a dose of 100 mg/day was approximately 40% lower than in a similarly studied group of younger (25 to 32 years old) individuals. Steady state, therefore, should be achieved after 2 to 3 weeks in older patients.

Liver Disease: As might be predicted from its primary site of metabolism, liver impairment can effect the elimination of sertraline. The elimination half-life of sertraline was prolonged in a single dose study of patients with mild, stable cirrhosis, with a mean of 52 hours compared to 22 hours seen in subjects without liver disease. This suggests that the use of sertraline in patients with liver disease must be approached with caution. If sertraline HCl is administered to patients with liver disease, a lower or less frequent dose should be used.

Renal Disease: The pharmacokinetics of sertraline HCl in patients with significant renal dysfunction have not been determined.

INDICATIONS

Depression

Freedep (Sertraline HCl) is indicated for the treatment of depression.

Obsessive-Compulsive Disorder

Freedep (Sertraline HCl) is indicated for the treatment of obsessions and compulsions in patients with obsessive-compulsive disorder (OCD), as defined in the DSM-III-R (i.e., the obsessions and compulsions cause marked distress, are time-consuming, or significantly interfere with social or occupational functioning.)

Panic Disorder

Freedep (Sertraline HCl) is indicated for the treatment of panic disorder, with or without agoraphobia, as defined in DSM-IV.

Posttraumatic Stress Disorder (PTSD)

Freedep (Sertraline HCl) is indicated for the treatment of Posttraumatic Stress Disorder (PTSD).

Premenstrual Dysphoric Disorder (PMDD)

Freedep (Sertraline HCl) is indicated for the treatment of Premenstural Dysphoric Disorder (PMDD).

DOSAGE AND ADMINISTRATION

Initial Treatment

Dosage for Adults

Major Depressive Disorder and Obsessive-Compulsive Disorder: Freedep (Sertraline HCl) treatment should be administered at a dose of 50 mg once daily.

Panic Disorder, Social Anxiety Disorder and PTSD: Freedep (Sertraline HCl) 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.

Premenstural Dysphoric Disorder: Freedep (Sertraline HCl) treatment should be initiated with a dose of 50 mg per day, either daily throughout the menstrual cycle or limited to the luteal phase of the menstrual cycle, depending on physician assessment. Patients not responding to a 50 mg/day dose may benefit from dose increase (at 50 mg increments/menstrual cycle) up to 150 mg per day when dosing daily throughout the menstrual cycle, or 100 mg per day when dosing during luteal phase of the menstrual cycle.

While a relationship between dose and effect has not been established for depression, OCD, or panic disorder, patients were dosed in a range of 50-200 mg/day in the clinical trials demonstrating the effectiveness of sertraline HCl for these indications. Consequently, a dose of 50 mg, administered once daily, is recommended as the initial dose. Patients not responding to a 50 mg dose may benefit from dose increases up to a maximum of 200 mg/day. Given the 24 hour elimination half-life of sertraline HCl, dose changes should not occur at intervals of less than 1 week.

Sertraline HCl should be administered once daily either in the morning or evening.

Dosage for Hepatically Impaired Patients

The use of Freedep (Sertraline HCl) in patients with liver disease should be approached with caution. The effects of sertraline in patients with moderate and severe hepatic impairment have not been studied. If sertraline is administered to patients with liver impairment, a lower or less frequent dose should be used.

Switching Patients to or from a Monoamine Oxidase Inhibitor

At least 14 days should elapse between discontinuation of a MAOI and initiation of therapy with Freedep (Sertraline HCl). In addition, at least 14 days should be allowed after stopping Freedep (Sertraline HCl) before starting a MAOI

SIDE EFFECTS

Those reported in placebo controlled clinical trials:

Autonomic Nervous System : Ejaculation failure, Increased sweating, Dry mouth
Central and Peripheral Nervous System : Dizziness, Tremors, Somnolence, Fatigue, Malaise
Gastrointestinal : Anorexia, Constipation, Diarrhea, Dyspepsia, Nausea
Psychiatric : Agitation, Insomnia, Decreased libido
Skin and Appendages : Rash
Special Senses : Abnormal Vision

Male and Female Sexual Dysfunction with SSRIs

Although changes in sexual desire, sexual satisfaction and sexual performance often occur as manifestations of a psychiatric disorder, they may also be a consequence of pharmacological treatment. In particular, some evidence suggests that selective serotonin reuptake inhibitors (SSRIs) can cause such untoward sexual experiences.

DRUG ABUSE AND DEPENDENCE

Controlled Substance Class: Freedep (Sertraline HCl) is not a controlled substance.

Physical and Psychological Dependence: Sertraline HCl has not been systematically studied, in animals or humans, for its potential for abuse, tolerance, or physical dependence. However, the premarketing clinical experience with sertraline HCl did not reveal any tendency for a withdrawal syndrome or any drug-seeking behavior. As with any new CNS active drug, physicians should carefully evaluate patients for history of drug abuse and follow such patients closely, observing them for signs of sertraline HCl misuse or abuse (e.g., development of tolerance, incrementation of dose, drug-seeking behavior).

DRUG INTERACTIONS

Potential Effects of Co administration of Drugs Highly Bound to Plasma Proteins: Because Freedep (Sertraline HCl) is tightly bound to plasma protein, the administration of sertraline HCl to a patient taking another drug which is tightly bound to protein, (e.g., warfarin, digitoxin) may cause a shift in plasma concentrations potentially resulting in an adverse effect. Conversely, adverse effects may result from displacement of protein bound sertraline HCl by other tightly bound drugs.

Cimetidine: In a study assessing disposition of sertraline HCl (100 mg) on the second of 8 days of cimetidine administration (800 mg daily), there were significant increases in sertraline HCl mean AUC (50%), C_{max} (24%) and half-life (26%) compared to the placebo group. The clinical significance of these changes is unknown.

CNS Active Drugs: In a study comparing the disposition of intravenously administered diazepam before and after 21 days of dosing with either sertraline HCl (50 to 200 mg/day escalating dose) or placebo, there was a 32% decrease relative to baseline in diazepam clearance for the sertraline HCl group compared to a 19% decrease relative to baseline for the placebo group ($p<0.03$). The clinical significance of these changes is unknown.

In a placebo-controlled trial in normal volunteers, the administration of two doses of sertraline HCl did not significantly alter steady-state lithium levels or the renal clearance of lithium. The risk of using sertraline HCl in combination with other CNS active drugs has not been systematically evaluated. Consequently, caution is advised if the concomitant administration of sertraline HCl and such drugs is required.

Monoamine Oxidase Inhibitors: See CONTRAINDICATIONS and WARNINGS.

Drugs Metabolized by Cytochrome P450 3A4: The results of two studies demonstrated that sertraline co-administration did not increase plasma concentrations of terfenadine or carbamazepine. These data suggest that sertraline HCl's extent of inhibition of P450 3A4 is not likely to be of clinical significance.

Drugs Metabolized by P450 2D6: Many antidepressants (e.g., the SSRIs) 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 concentrations of co-administered drugs that are metabolized by P450 2D6. The drugs for which this potential interaction is of greatest concern are those metabolized primarily by 2D6 and which have a narrow therapeutic index (e.g., the tricyclic antidepressants and the type 1C antiarrhythmics propafenone and flecainide). The extent to which this interaction is an important clinical problem depends on the extent of the inhibition of P450 2D6 by the antidepressant and the therapeutic index of the co-administered drug. There is variability among the antidepressants in the extent of clinically important 2D6 inhibition, and in fact sertraline at lower doses has a less prominent inhibitory effect on 2D6 than some others in the class. Nevertheless, even sertraline has the potential for clinically important 2D6 inhibition. Consequently, concomitant use of a drug metabolized by P450 2D6 with sertraline HCl may require lower doses than usually prescribed for the other drug. Furthermore, whenever sertraline is withdrawn from co-therapy, an increased dose of the co-administered drug may be required (see Tricyclic Antidepressants - below).

Tricyclic Antidepressants (TCAs): The extent to which SSRI TCA interactions may pose clinical problems will depend on the degree of inhibition and the pharmacokinetics of the SSRI involved. Nevertheless, caution is indicated in the co-administration of TCAs with sertraline HCl, because sertraline HCl may inhibit TCA metabolism. Plasma TCA concentrations may need to be monitored, and the dose of TCA may need to be reduced, if a TCA is co-administered with sertraline HCl (see Drugs Metabolized by P450 2D6 - above).

Sumatriptan: There have been rare postmarketing reports describing patient with weakness, hyperreflexia, and incoordination following the use of a selective serotonin reuptake inhibitor (SSRI) and sumatriptan. If concomitant treatment with sumatriptan and an SSRI (e.g.,

citalopram, fluoxetine, fluvoxamine, paroxetine, sertraline) is clinically warranted, appropriate observation of the patient is advised.
Hypoglycemic Drugs: In a placebo-controlled trial in normal volunteers, administration of sertraline HCl for 22 days (including 200 mg/day for the final 13 days) caused a statistically significant 16% decrease from baseline in the clearance of tolbutamide following an intravenous 1000 mg dose. Sertraline HCl administration did not noticeably change either the plasma protein binding or the apparent volume of distribution of tolbutamide, suggesting that the decreased clearance was due to a change in the metabolism of the drug. The clinical significance of this decrease in tolbutamide clearance is unknown.
Atenolol: Sertraline HCl (100 mg) when administered to 10 healthy male subjects had no effect on the beta-adrenergic blocking ability of atenolol.
Digoxin: In a placebo-controlled trial in normal volunteers, administration of sertraline HCl for 17 days (including 200 mg/day for the last 10 days) did not change serum digoxin levels on digoxin renal clearance.

WARNINGS
Cases of serious, sometimes fatal, reactions have been reported in patients receiving sertraline HCl in combination with a monoamine oxidase inhibitor (MAOI). Symptoms of a drug interaction between an SSRI and an MAOI include: hyperthermia, rigidity, myocionus, autonomic instability with possible rapid fluctuations of vital signs, mental status changes that include confusion, irritability, and extreme agitation progressing to delirium and coma. These reactions have also been reported in patients who have recently discontinued an SSRI and have been started on an MAOI. Some cases presented with features resembling neuroleptic malignant syndrome. Therefore, it is recommended that sertraline HCl not be used in combination with an MAOI, or within 14 days of discontinuing treatment with an MAOI. Similarly, at least 14 days should be allowed after stopping sertraline HCl before starting an MAOI.

PRECAUTIONS
General
Activation of Mania/Hypomania: During premarketing testing, hypomania or mania occurred in approximately 0.4% of sertraline HCl treated patients.
Weight Loss: Significant weight loss may be an undesirable result of treatment with Freedep (Sertraline HCl) for some patients, but on average, patients in controlled trials had minimal, 1 to 2 pound weight loss, versus smaller changes on placebo. Only rarely have sertraline patients been discontinued for weight loss.
Seizure: Sertraline HCl has not been evaluated in patients with a seizure disorder. These patients were excluded from clinical studies during the product's premarket testing. No seizures were observed among approximately 3000 patients treated with sertraline HCl 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%. Accordingly, sertraline HCl 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. Close supervision of high risk patients should accompany initial drug therapy. Prescriptions for Freedep (Sertraline HCl) should be written for the smallest quantity of tablets consistent with good patient management, in order to reduce the risk of overdose.
Weak Uricosuric Effect: Sertraline HCl is associated with a mean decrease in serum uric acid of approximately 7%. The clinical significance of this weak uricosuric effect is unknown, and there have been no reports of acute renal failure with sertraline HCl.
Use in Patients with Concomitant Illness: Clinical experience with sertraline HCl in patients with certain concomitant systemic illness is limited. Caution is advisable in using sertraline HCl in patients with diseases or conditions that could affect metabolism or hemodynamic responses.
Sertraline HCl 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 774 patients who received sertraline HCl in double-blind trials were evaluated and the data indicate that sertraline HCl is not associated with the development of significant ECG abnormalities.
Sertraline HCl is extensively metabolized by the liver. In patients with chronic mild liver impairment, sertraline clearance was reduced, resulting in increased AUC, C_{max}, and elimination half-life. The effects of sertraline in patients with moderate and severe hepatic impairment have not been studied. The use of sertraline in patients with liver disease must be approached with caution. If sertraline is administered to patients with liver impairment, a lower or less frequent dose should be used.
Since sertraline HCl is extensively metabolized, excretion of unchanged drug in urine is a minor route of elimination. A clinical study comparing sertraline pharmacokinetics in healthy volunteers to that in patients with renal impairment ranging from mild to severe (requiring dialysis) indicated that the pharmacokinetics and protein binding are unaffected by renal disease. Based on the pharmacokinetics results, there is no need for dosage adjustment in patients with renal impairment.
Interference with Cognitive and Motor Performance: In controlled studies, sertraline HCl did not cause sedation and did not interfere with psychomotor performance.
Hyponatremia: Several cases of hyponatremia have been reported and appeared to be reversible when sertraline HCl 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 HCl. While there have been reports of abnormal bleeding or purpura in several patients taking sertraline HCl, it is unclear whether sertraline HCl had a causative role.

Pregnancy, Teratogenic Effects, Pregnancy Category C
Reproduction studies have been performed in rats and rabbits at doses up to 80 mg/kg/day and 40 mg/kg/day, respectively. These doses correspond to approximately 4 times the maximum recommended human dose (MRHD) on a mg/m2 basis. There was no evidence of teratogenicity at any dose level. There are no adequate and well controlled studies in pregnant women. Sertraline HCl should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers
It is not known whether, and if so in what amount, sertraline or its metabolites are excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Freedep (Sertraline HCl) is administered to a nursing woman.

Geriatric Use
Several hundred elderly patients have participated in clinical studies with sertraline HCl. The pattern of adverse reactions in the elderly was similar to that in younger patients.

OVERDOSE
Human Experience: In those cases of overdose involving only sertraline HCl, the reported doses ranged from 500 mg to 6000 mg. Symptoms of overdose with sertraline HCl alone included somnolence, nausea, vomiting, tachycardia, ECG changes, anxiety and dilated pupils. Treatment was primarily supportive and included monitoring of and use of activated charcoal, gastric lavage or cathartics and hydration. Although there were no reports of death when sertraline HCl was taken alone, there were 4 deaths involving overdoses of sertraline HCl in combination with other drugs and/or alcohol. Therefore, any overdose should be treated aggressively.
Management of Overdoses: Treatment should consist of those general measures employed in the management of over dosage with any antidepressant.
Ensure an adequate airway, oxygenation, and ventilation. Monitor cardiac rhythm and vital signs. General supportive and symptomatic measures are also recommended. Induction of emesis is not recommended. Gastric lavage with a large-bore orogastric tube with appropriate airway protection, if needed, may be indicated if performed soon after ingestion, or in symptomatic patients.
Activated charcoal should be administered. Due to the large volume of distribution of this drug, forced diuresis, dialysis, hemoperfusion, and exchange transfusion are unlikely to be of benefit. No specific antidotes for sertraline are known.
In managing overdosage, consider the possibility of multiple drug involvement. The physician should consider contacting a poison control center on the treatment of any overdose.

CONTRAINDICATIONS
Concomitant use in patients taking monoamine oxidase inhibitors (MAOIs) is contraindicated (see WARNINGS).
Freedep is contraindicated in patients with a hypersensitivity to sertraline or any of the inactive ingredients in Freedep.

PATIENT INFORMATION
Freedep (Sertraline HCl) is used for the treatment of Depression, Obsessive Compulsive Disorder, and Panic Disorder.
Do not take this medication if you are taking MAO Inhibitors.
Inform your doctor if you are pregnant or breast feeding. Freedep (Sertraline HCl) may cause dizziness, use caution while driving or operating hazardous machinery. This medication may cause stomach upset, nausea, diarrhea, dizziness, tremor, insomnia, sleepiness, sweating, dry mouth, and male sexual dysfunction. Inform your physician or pharmacist if these occur.

PRESENTATION
Freedep (Sertraline HCl) 50 mg in blister pack of 30 (3X10's) tablets
Freedep (Sertraline HCl) 100 mg in blister pack of 20 (2X10's) tablets

Dosage & Instructions:
As advised by the physician.
Keep all medicines out of the reach of children.
To be sold on the prescription of a registered medical practitioner only.
Protect from heat, light and moisture.
Store below 30°C.

خوراک وہدایات:
ڈاکٹر کی ہدایات کے مطابق استعمال کریں۔
تمام دوائیں بچّوں کی پہنچ سے دُور رکھیں۔
صرف رجسٹرڈ ڈاکٹر کے نسخہ پر ہی فروخت کی جائے۔
روشنی، گرمی اور نمی سے محفوظ، 30°C سے کم درجہ حرارت پر رکھیں۔