SOLOTIK®

Sertraline HCl

ACTION

Solotik (sertraline hydrochloride) is an antidepressant for oral administration.

PHARMACOLOGICAL and PHARMACOKINETICS CHARACTERISTICS

Pharmacological properties

Depression is known to be associated with a defect in serotonin (5-HT) metabolism in the brain. Both in vitro and in vivo sertraline is a potent and specific inhibitor of neuronal 5-HT uptake. It is devoid of stimulant, sedative or anticholinergic activity or cardiotoxicity in animals and in man. It has a neutral psychomotor profile. In accord with its selective inhibition of 5-HT uptake, sertraline does not enhance catecholaminergic activity and has no affinity for muscarinic, serotonergic, adrenergic or GABA receptors. Chronic administration of sertraline was associated with down-regulation of noradrenergic and serotonergic receptors, as observed with clinically effective antidepressants or anobsessional drugs.

Pharmacokinetics properties

After oral administration of sertraline, in man, peak blood levels occur at about 6-8 hours. Approximately 98% of the circulating drug is bound to plasma proteins. The plasma half-life of sertraline is approximately 26 hours, and the half-life of the principal metabolite in plasma, desmethylsertraline is approximately 62-104 hours. The metabolite is inactive in vivo tests.

Sertraline and desmethylsertraline are both extensively metabolized in man and the resultant metabolites excreted in the feces and urine in equal amounts. Only a small amount of unchanged sertraline is excreted in the urine.

Food does not significantly change the bioavailability of Solotik tablets. Solotik has not been observed to produce physical or psychological dependence.

INDICATIONS

Solotik is indicated in the treatment of depression. Following satisfactory response, continuation with Solotik therapy is effective in preventing relapse of the initial episode of depression or recurrence of further depression episodes. Solotik is also indicated for the treatment of obsessive-compulsive disorders.

DOSAGE AND ADMINISTRATION

Solotik should be given as a single dose. Solotik tablets can be administered with or without food.

The therapeutic dose is 50mg/day. This dose may be increased in case of lack of response in 50 mg increments (at intervals of at least 1 week) to a maximum of 200mg/day. The onset of therapeutic effects may be seen within 7 days, although 2-4 weeks (and even longer in obsessive-compulsive disorders) are usually necessary for full antidepressant activity. The same dose range may be used in both elderly and younger adult patients. Dosage during prolonged maintenance therapy should be kept at the lowest effective level, with subsequent adjustment depending on therapeutic response.

CONTRAINDICATIONS

Hypersensitivity to the drug components or to other agents which are closely related from a chemical point of view. Solotik is generally contraindicated during pregnancy and lactation and in patients with a recent history of myocardial infarction or unstable heart diseases. Concomitant use of Solotik in patients taking monoamine oxidase inhibitors (MAOI) is contraindicated.

Use of Solotik should be avoided in patients with unstable epilepsy. Concomitant use of Solotik with Serotonergic drugs, such as Trytophan or Fenfluramine is contraindicated. Solotik should not be administered to patients receiving electroconvulsive therapy (ECT).

WARNINGS AND PRECAUTIONS

Solotik has not been evaluated or used to any applicable extent in patients with a recent myocardial infarctions or unstable heart disease.

Use in children

The safety and effectiveness of Solotik in children have not been established, and therefore the use of Solotik in children should be avoided.

Use in elderly

The pattern and incidence of adverse reactions in elderly was similar to that in younger patients.

Use in hepatic insufficiency

Solotik is extensively metabolized in 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 subject. Therefore, Solotik should be used with caution in patients with hepatic disease. If Solotik is administered to patients with hepatic impairment, lower or less frequent doses should be considered.

Use in renal insufficiency

Since Solotik is extensively metabolized, excretion of unchanged drug in urine is a minor route of elimination. In fact, in patients with mild to moderate renal impairment (creatinine clearance 20-50ml/min) or severe renal impairment (creatinine clearance 20 ml/min), single dose pharmacokinetic parameters were not significantly different compared to controls. However, steady-state pharmacokinetics of Solotik have not been adequately studied in this patient population; therefore, Solotik should be used with caution in such patients.

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. Solotik should be prescribed for the smallest quantity in order to reduce the risk of overdose.

Seizures

Patients with controlled epilepsy who are undergoing a treatment with Solotik should be carefully monitored. The drug should be discontinued in any patient who develop seizures.

Uricosuric effect

Solotik is associated with mean decrease in serum uric acid of approximately 7%. The clinical significance of this uricosuric effect is unknown. There have been no reports of acute renal failure with Solotik.

Use in patients with concomitant illnesses

Clinical experience with Solotik in patients with concomitant systemic illnesses is limited. Caution is advisable in using Solotik in patients with diseases or conditions that could affect metabolism or hemodynamic response.

Solotik has not been evaluated or used to any appreciable extent in patients with a recent history or myocardial infarction or unstable heart disease. Patients with these diagnoses were excluded from clinical studies during the products premarketing testing. However, the electro cardiograms of 774 patients who received sertraline in double-blind trials were evaluated and the data indicate that sertraline is not associated with the development of significant ECG abnormalities.

Physical and psychological dependence

Solotik has not been systematically studied in animals or humans for its potential for abuse, tolerance or physical dependence. As with any new CNS active drugs, physicians should carefully evaluate patients for history of drug abuse and follow such patients closely, observing them for signs of Solotik misuse or abuse (e.g., development of tolerance, incrementation of dose, drug-seeking behavior).

Concomitant treatment with MAOI

Cases of serious reactions have been reported in patients receiving Solotik in combination with a monoamine oxidase inhibitor, including the selective inhibitor, selegiline, and the reversible inhibitor, moclobemide. Some of these patients presented with features resembling neuroleptic malignant syndrome (serotonin syndrome).

Similar cases, sometimes fatal have been reported in patients receiving other antidepressants in combination with a monoamine oxidase inhibitor (MAOI). Such reactions have also been reported in patients who have recently discontinued an antidepressant or antiobsessional drug and have been started on a MAOI. Therefore, Solotik should not be used in combination with MAOI or within 14 days of discontinuing treatment with a MAOI. Similarly, at least 14 days should elapse after discontinuing Solotik before starting a MAOI.

Drug Interactions

Since Solotik is bound to plasma proteins, the potential of Solotik to interact with other plasma protein bound drugs should be borne in mind. Drug interaction studies have been performed with sertraline and other drugs. Small statistically significant changes in some pharmacokinetic parameters were observed with diazepam and tolbutamide. Their clinical significance is unknown. Coadministration of Solotik and cimetidine caused a substantial decrease in Solotik clearance of unknown clinical significance. Co-administration with warfarin resulted in a small but statistically significant increase in prothrombin time, the clinical significance of which is unknown. Accordingly, prothrombin time should be carefully monitored when Solotik therapy is initiated or stopped.

Solotik has no effect on the beta-adrenergic blocking ability of atenolol. No interaction was observed with glibenclamide or digoxin.

CNS active drugs

Monoamine Oxidase Inhibitors (MAOI):

Based on experience with combined administration of MAOI and antidepressants, at least 14 days should elapse between discontinuation of MAOI and initiation of treatment of Solotik and vice versa.

Lithium:

Interaction studies with lithium showed no clinically or statistically significant changes of the steady state lithium plasma concentrations and renal lithium clearance. However, co-administration with lithium may lead to a higher incidence of serotonin-associated side effects.

Therefore, it is recommended that plasma lithium levels be monitored following initiation of Solotik therapy, so that appropriate adjustments to the lithium dose may be made if necessary.

There is no experience of concomitant use of Solotik with lithium in depressed patients.

Serotonergic drugs:

There is limited controlled experience regarding the optimal timing of switching from other antidepressant or antiobsessional drugs to Solotik. Care and prudent medical judgment should be exercised when switching, particularly from long acting agents. The duration of wash-out period which should intervene before switching from one selective serotonin reuptake inhibitor (SSRI) to another has not been established. Until further data are available, serotonergic drugs such as tryptophan or fenfluramine, should not be used concomitantly with Solotik.

The possible risks related to a concomitant therapy with other CNS active drugs have not been systematically assessed. Therefore this combination requires particular caution and vigilance from the physician, so as to avoid unexpected drug interactions.

Electroconvulsive therapy

In patients receiving electroconvulsive therapy (ECT), concomitant administration of Solotik should be avoided due to lack of experience in this situation.

Alcohol

Co-administration of Solotik and alcohol did not potentiate the effects of alcohol on cognitive and psychomotor performance in healthy subjects; however, the concomitant use of Solotik and alcohol in depressed patients should be avoided.

Microsomal enzyme induction

Preclinical studies showed that Solotik activated microsomal hepatic enzymes. Clinical studies showed that Solotik causes a minor hepatic enzyme activation as showed by the slight (5%) but statistically significant decrease in the antipyrine half-life following an administration of 200mg/day for 21 days.

This small change of the antipyrine-half life reflects a clinically insignificant change in hepatic metabolism.

Pregnancy and lactation

No data concerning Solotik levels in breast milk are available.

A decrease in fertility was observed in one of two studies conducted in rats at doses of 80 mg/kg (20 times the maximum daily human dose in mg/kg and 4 times in mg/m²).

Teratogenic effects

Reproduction studies have been performed in rats and rabbits at doses up to approximately 20 and 10 times the maximum daily human dose in mg/kg (44.5 times the dose in mg/m²). There was no evidence of teratogenicity at any dose level.

At the dose level corresponding to approximately 2.5-10 times the maximum daily human dose, however, Solotik caused maternal toxicity which in turn delayed ossification processes in the fetuses.

There are no adequate studies in pregnant women. Because animal reproduction studies are not always predicative of human response, Solotik should be used during pregnancy only if clearly needed and under a close medical control.

Non teratogenic effects

In animal studies, there was a decreased neonatal survival following maternal administration of Solotik at doses approximately 5 times the maximum therapeutic daily dose in mg/kg. The decrease in neonatal survival was probably due to Solotik exposure in the uterus. The clinical significance of these effects is unknown.

Effect on ability to drive and use machines

Clinical Pharmacology studies have shown that Solotik has no effect on psychomotor performance. There is no evidence that Solotik enhances the CNS depressant effects of benzodiazepines, or other tranquilizers, or alcohol. However, as antidepressant or antiobsessional drugs may impair the mental or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery, the patients should be cautioned accordingly.

SIDE EFFECTS

The most common events occurred during premarketing clinical trials are the following:

Autonomic Nervous System Disorders: Dry Mouth, Increased sweating.

Cardiovascular Disorders: Palpitations, Chest pain. Central and Peripheral Nervous System *Disorders:* Headache, Dizziness, Tremor, Paresthesia, Hypoesthesia, Twitching, Hypertonia.

Disorders of Skin and Appendages: Rash.

Gastrointestinal Disorders: Nausea, Diarrhea/Loose stools, Constipation, Dyspepsia, Emesis, Flatulence, Anorexia, Abdominal Pain, Increased Appetite.

General Disorders: Fatigue, Flushing, Fever, Backache.

Metabolic and Nutritional Disorders: Thirst.

Musculoskeletal System Disorders: Myalgia.

Psychiatric Disorders: Insomnia, Sexual dysfunctions (primarily ejaculatory delay). Somnolence, Agitation, Nervousness, Anxiety, Yawning, Concentration difficulties.

Reproductive System: Menstrual disorders.

Respiratory System Disorders: Rhinitis, Pharyngitis.

Sense Organs: Slight anomalies, Tinnitus, Taste deviation.

Urinary System Disorders: Micturition frequency disorder and micturition disorder.

Laboratory Tests:

In man, asymptomatic elevations in serum transaminases SGOT (or AST) and SGPT (or ALT) have been rarely reported. These hepatic enzyme elevations usually occurred within the first 1 to 9 weeks of drug treatment and promptly diminished upon drug discontinuation.

Solotik therapy was associated with small mean increases in total cholesterol and triglycerides and a small mean decrease in serum uric acid of no apparent clinical importance.

Rare cases of hyponatremia have been reported (mostly in elderly patients under treatment with diuretics or other drugs) which appeared to be reversible when Solotik was discontinued. Some cases were possibly due to syndrome of inappropriate antidiuretic hormone secretion.

The side-effect profile commonly observed in double-blind ,well controlled studies in patients with obsessive-compulsive disorders was similar to that observed in clinical trials in patients with depression.

Activation of Mania/Hypomania

During premarketing testing, hypomania occurred in 0.4% of patients treated with sertraline. Activation of mania/hypomania has also been reported in a small proportion of patients with major affective disorders treated with other marketed antidepressants or other antiobsessional drugs.

Weight Loss

Significant weight loss may be observed in some patients treated with Solotik, patients treated in controlled clinical trials had minimum weight loss (at the most 2 pounds), versus smaller changes on placebo. Only, rarely has the patients to discontinue the treatment on account of weight loss.

Since market introduction, in addition to the above mentioned adverse events which occurred during pre-marketing clinical trials, other adverse events have been reported; however, a casual relation to Solotik cannot be established. Among these the following are included: extrapyramidal symptoms, convulsions, gait abnormalities, hyperprolactinemia, galactorrhea and rare episodes of erythema multiform.

Rare cases of withdrawal reactions have been reported: hallucinations, aggressive reactions and psychosis and cannot be distinguished from the natural history of the underlying disease.

OVERDOSAGE

On evidence available, Solotik has a wide margin of safety in overdose. Serious sequelae have not been reported following overdose of Soiotik alone up to 6 grams, while this occurred in combination with other drugs and/or alcohol. Therefore, any overdosage should be treated aggressively. No specific therapy is recommended and there are no specific antidotes to Solotik.

In case of overdosage, establish and maintain an airway, insure adequate oxygenation and ventilation. Activated charcoal, which may be used with sorbitol, may be as or more effective than emesis or lavage, and should be considered in treating overdose.

Cardiac and vital signs monitoring is recommended along with general symptomatic and supportive measures.

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

PRESENTATIONS

Tablets:

SOLOTIK 50: Sertraline (as HCl) 50 mg/tablet

Excipients: *Sodium starch glycolate, povidone, microcrystalline cellulose, magnesium stearate, opadry II blue.*

SOLOTIK 100: Sertraline (as HCl) 100 mg/tablet

Excipients: *Sodium starch glycolate, povidone, microcrystalline cellulose, magnesium stearate, opadry II yellow.*

THIS IS A MEDICAMENT

- A medicament is a product which affects your health, and its consumption contrary to instructions is dangerous.
- Follow the doctor's prescription strictly, the method of use and the instructions of the pharmacist who sold the medicament.
- The doctor and the pharmacist are experts in medicine, its benefits and risks.
- Do not by yourself interrupt the period of treatment prescribed for you.
- Do not repeat the same prescription without consulting your doctor.

Manufactured by:
HIKMA Pharmaceuticals, Amman-Jordan

Keep medicament out of the reach of children

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