NOVARTIS

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SERENTIL®

(mesoridazine besylate) Tablets, USP

(mesoridazine besylate) Injection, USP

(mesoridazine besylate) Oral Solution, USP

Rx only

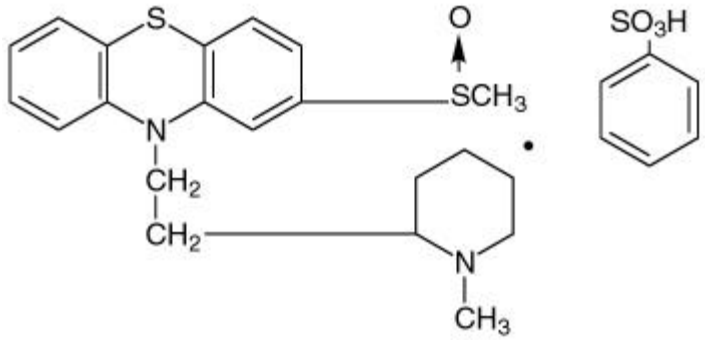
Prescribing Information

WARNING

SERENTIL® (MESORIDAZINE BESYLATE) HAS BEEN SHOWN TO PROLONG THE QTc INTERVAL IN A DOSE RELATED MANNER, AND DRUGS WITH THIS POTENTIAL, INCLUDING SERENTIL, HAVE BEEN ASSOCIATED WITH TORSADE DE POINTES-TYPE ARRHYTHMIAS AND SUDDEN DEATH. DUE TO ITS POTENTIAL FOR SIGNIFICANT, POSSIBLY LIFE-THREATENING, PROARRHYTHMIC EFFECTS, SERENTIL SHOULD BE RESERVED FOR USE IN THE TREATMENT OF SCHIZOPHRENIC PATIENTS WHO FAIL TO SHOW AN ACCEPTABLE RESPONSE TO ADEQUATE COURSES OF TREATMENT WITH OTHER ANTIPSYCHOTIC DRUGS, EITHER BECAUSE OF INSUFFICIENT EFFECTIVENESS OR THE INABILITY TO ACHIEVE AN EFFECTIVE DOSE DUE TO INTOLERABLE ADVERSE EFFECTS FROM THOSE DRUGS. (SEE WARNINGS, CONTRAINDICATIONS, AND INDICATIONS.)

DESCRIPTION

Serentil® (mesoridazine besylate), the besylate salt of a metabolite of thioridazine, is a phenothiazine tranquilizer. Serentil is 10-[2(1-methyl-2-piperidyl)ethyl]-2-(methyl-sulfinyl)-phenothiazine [as the besylate].



Tablet, 10 mg, for oral administration

ACTIVE INGREDIENT: mesoridazine (as the besylate), 10 mg.

INACTIVE INGREDIENTS: acacia, carnauba wax, colloidal silicon oxide, FD&C Red No. 40 aluminum lake, lactose, microcrystalline cellulose, povidone, sodium benzoate, starch, stearic acid, sucrose, synthetic black iron oxide, talc, titanium dioxide and other ingredients.

Tablet, 25 mg, for oral administration

ACTIVE INGREDIENT: mesoridazine (as the besylate), 25 mg.

INACTIVE INGREDIENTS: acacia, carnauba wax, colloidal silicon oxide, FD&C Red No. 40 aluminum lake, lactose, microcrystalline cellulose, povidone, sodium benzoate, starch, stearic acid, sucrose, synthetic black iron oxide, talc, titanium dioxide and other ingredients.

Tablet, 50 mg, for oral administration

ACTIVE INGREDIENT: mesoridazine (as the besylate), 50 mg.

INACTIVE INGREDIENTS: acacia, carnauba wax, colloidal silicon oxide, FD&C Red No. 40 aluminum lake, gelatin, lactose, microcrystalline cellulose, povidone, sodium benzoate, starch, stearic acid, sucrose, synthetic black iron oxide, talc, titanium dioxide and other ingredients.

Tablet, 100 mg, for oral administration

ACTIVE INGREDIENT: mesoridazine (as the besylate), 100 mg.

INACTIVE INGREDIENTS: acacia, carnauba wax, colloidal silicon oxide, FD&C Red No. 40 aluminum lake, gelatin, lactose, microcrystalline cellulose, povidone, sodium benzoate, starch, stearic acid, sucrose, synthetic black iron oxide, talc, titanium dioxide and other ingredients.

Ampuls, 1 mL, for Intramuscular administration

ACTIVE INGREDIENT: mesoridazine (as the besylate), 25 mg.

INACTIVE INGREDIENTS: edetate disodium USP, 0.5 mg; sodium chloride USP, 7.2 mg; carbon dioxide gas (bone dry) q.s.; water for injection USP, q.s. to 1 mL.

Concentrate, for oral administration

ACTIVE INGREDIENT: mesoridazine (as the besylate), 25 mg per mL.

INACTIVE INGREDIENTS: alcohol, 0.61% by volume; citric acid; FD&C Red No. 40; flavors; methylparaben; propylparaben; purified water; sodium citrate; sorbitol.

CLINICAL PHARMACOLOGY

The basic pharmacological activity of Serentil® (mesoridazine besylate) is similar to that of other phenothiazines.

However, mesoridazine has been shown to prolong the QTc interval in a dose-dependent fashion. This effect may increase the risk of serious, potentially fatal, ventricular

arrhythmias, such as torsade de pointes-type arrhythmias. Due to this risk, Serentil is indicated only for schizophrenic patients who have not been responsive to or cannot tolerate other antipsychotic agents (see WARNINGS and CONTRAINDICATIONS).

However, the prescriber should be aware that Serentil has not been systematically evaluated in controlled trials in treatment of refractory schizophrenic patients and its efficacy in such patients is unknown.

INDICATIONS

Serentil® (mesoridazine besylate) is indicated for the management of schizophrenic patients who fail to respond adequately to treatment with other antipsychotic drugs. Due to the risk of significant, potentially life-threatening, proarrhythmic effects with Serentil treatment, Serentil should be used only in patients who have failed to respond adequately to treatment with appropriate courses of other antipsychotic drugs, either because of insufficient effectiveness or the inability to achieve an effective dose due to intolerable adverse effects from those drugs. Consequently, before initiating treatment with Serentil, it is strongly recommended that a patient be given at least two trials, each with a different antipsychotic drug product at an adequate dose, and for an adequate duration (see WARNINGS and CONTRAINDICATIONS).

However, the prescriber should be aware that Serentil has not been systematically evaluated in controlled trials in treatment of refractory schizophrenic patients and its efficacy in such patients is unknown.

CONTRAINDICATIONS

Serentil® (mesoridazine besylate) use should be avoided in combination with other drugs that are known to prolong the QTc interval and in patients with congenital long QT syndrome or a history of cardiac arrhythmias (see WARNINGS and PRECAUTIONS).

As with other phenothiazines, Serentil is contraindicated in severe central nervous system depression or comatose states from any cause including drug induced central nervous system depression (see WARNINGS).

Serentil is contraindicated in individuals who have previously shown hypersensitivity to the drug.

WARNINGS

Potential for Proarrhythmic Effects

DUE TO THE POTENTIAL FOR SIGNIFICANT, POSSIBLY LIFE-THREATENING, PROARRHYTHMIC EFFECTS WITH SERENTIL® (MESORIDAZINE BESYLATE) TREATMENT, SERENTIL SHOULD BE RESERVED FOR USE IN THE TREATMENT OF SCHIZOPHRENIC PATIENTS WHO FAIL TO SHOW AN ACCEPTABLE RESPONSE TO ADEQUATE COURSES OF TREATMENT WITH OTHER ANTIPSYCHOTIC DRUGS, EITHER BECAUSE OF INSUFFICIENT EFFECTIVENESS OR THE INABILITY TO ACHIEVE AN EFFECTIVE DOSE DUE TO INTOLERABLE ADVERSE

EFFECTS FROM THOSE DRUGS. CONSEQUENTLY, BEFORE INITIATING TREATMENT WITH SERENTIL, IT IS STRONGLY RECOMMENDED THAT A PATIENT BE GIVEN AT LEAST TWO TRIALS, EACH WITH A DIFFERENT ANTIPSYCHOTIC DRUG PRODUCT, AT AN ADEQUATE DOSE, AND FOR AN ADEQUATE DURATION. SERENTIL HAS NOT BEEN SYSTEMATICALLY EVALUATED IN CONTROLLED TRIALS IN THE TREATMENT OF REFRACTORY SCHIZOPHRENIC PATIENTS AND ITS EFFICACY IN SUCH PATIENTS IS UNKNOWN.

A study in nine chronic schizophrenic patients who were treated with mesoridazine 75 mg/day for the first week, 200 mg/day during week 2, and 300 mg/day during weeks 3 and 4, revealed evidence of a dose-related prolongation of the QT interval. All patients had a normal ECG at baseline and eight of the nine had normal ECG's two weeks after drug discontinuation.

Prolongation of the QTc interval has been associated with the ability to cause torsade de pointes-type arrhythmias, a potentially fatal polymorphic ventricular tachycardia, and sudden death. There are published case reports of ventricular tachycardia, in one case with a fatal outcome, in association with mesoridazine overdosage. A causal relationship between these events and Serentil therapy has not been established but, given the ability of Serentil to prolong the QTc interval, such a relationship is possible.

Certain circumstances may increase the risk of torsade de pointes and/or sudden death in association with the use of drugs that prolong the QTc interval, including 1) bradycardia, 2) hypokalemia, 3) concomitant use of other drugs that prolong the QTc interval, and 4) presence of congenital prolongation of the QT interval (see CONTRAINDICATIONS and PRECAUTIONS).

It is recommended that patients being considered for Serentil treatment have a baseline ECG performed and serum potassium levels measured. Serum potassium should be normalized before initiating treatment and patients with a QTc interval greater than 450 msec should not receive Serentil treatment. It may also be useful to periodically monitor ECG's and serum potassium during Serentil treatment especially during a period of dose adjustment. Serentil should be discontinued in patients who are found to have a QTc interval over 500 msec.

Patients taking Serentil who experience symptoms that may be associated with the occurrence of torsade de pointes (e.g., dizziness, palpitations, or syncope) may warrant further cardiac evaluation; in particular, Holter monitoring should be considered.

Tardive Dyskinesia

Tardive dyskinesia, a syndrome consisting of potentially irreversible, involuntary, dyskinetic movements, may develop in patients treated with antipsychotic drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of antipsychotic treatment, which patients are likely to develop the syndrome. Whether antipsychotic drug products differ in their potential to cause tardive dyskinesia is unknown.

Both the risk of developing the syndrome and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose

of antipsychotic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses.

There is no known treatment for established cases of tardive dyskinesia, although the syndrome may remit, partially or completely, if antipsychotic treatment is withdrawn. Antipsychotic treatment, itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome and thereby may possibly mask the underlying disease process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown.

Given these considerations, antipsychotic should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic antipsychotic treatment should generally be reserved for patients who suffer from a chronic illness 1) that is known to respond to antipsychotic drugs, and 2) for which alternative, equally effective but potentially less harmful treatments are not available or appropriate. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically.

If signs and symptoms of tardive dyskinesia appear in a patient on antipsychotic, drug discontinuation should be considered. However, some patients may require treatment despite the presence of the syndrome.

(For further information about the description of tardive dyskinesia and its clinical detection, please refer to the sections on Information for Patients and Adverse Reactions.)

Neuroleptic Malignant Syndrome (NMS)

A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with antipsychotic drugs. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmias).

The diagnostic evaluation of patients with this syndrome is complicated. In arriving at a diagnosis, it is important to identify cases where the clinical presentation includes both serious medical illness (e.g., pneumonia, systemic infection, etc.) and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever and primary central nervous system (CNS) pathology.

The management of NMS should include 1) immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy, 2) intensive symptomatic treatment and medical monitoring, and 3) treatment of any concomitant serious medical problems for which specific treatments are available. There is no general agreement about specific pharmacological treatment regimens for uncomplicated NMS.

If a patient requires antipsychotic drug treatment after recovery from NMS, the potential reintroduction of drug therapy should be carefully considered. The patient should be carefully monitored, since recurrences of NMS have been reported.

Where patients are participating in activities requiring complete mental alertness, (e.g., driving) it is advisable to administer the phenothiazines cautiously and to increase the dosage gradually.

Central Nervous System Depressants

As in the case of other phenothiazines, Serentil is capable of potentiating central nervous system depressants (e.g., alcohol, anesthetics, barbiturates, narcotics, opiates, other psychoactive drugs, etc.) as well as atropine and phosphorus insecticides. Severe respiratory depression and respiratory arrest have been reported when a patient was given Serentil and a concomitant high dose of a barbiturate.

PRECAUTIONS

While ocular changes have not to date been related to Serentil® (mesoridazine besylate), one should be aware that such changes have been seen with other drugs of this class.

Because of possible hypotensive effects, reserve parenteral administration for bedfast patients or for acute ambulatory cases, and keep patient lying down for at least one-half hour after injection.

Leukopenia and/or agranulocytosis have been attributed to phenothiazine therapy. A single case of transient granulocytopenia has been associated with Serentil. Since convulsive seizures have been reported, patients receiving anticonvulsant medication should be maintained on that regimen while receiving Serentil.

Antipsychotic drugs elevate prolactin levels; the elevation persists during chronic administration. Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin dependent in vitro, a factor of potential importance if the prescription of these drugs is contemplated in a patient with a previously detected breast cancer. Although disturbances such as galactorrhea, amenorrhea, gynecomastia, and impotence have been reported, the clinical significance of elevated serum prolactin levels is unknown for most patients. An increase in mammary neoplasms has been found in rodents after chronic administration of antipsychotic drugs. Neither clinical studies nor epidemiologic studies conducted to date, however, have shown an association between chronic administration of these drugs and mammary tumorigenesis; the available evidence is considered too limited to be conclusive at this time.

Drug Interactions

There are no studies of the coadministration of mesoridazine and other drugs which prolong the QTc interval. However, it is expected that such coadministration would produce additive prolongation of the QTc interval and, thus, such use is contraindicated (see WARNINGS and CONTRAINDICATIONS).

Information for Patients

Patients should be informed that Serentil has been associated with potentially fatal heart rhythm disturbances. The risk of such events may be increased when certain drugs are given together

with Serentil. Therefore, patients should inform the prescriber that they are receiving Serentil treatment before taking any new medication.

Given the likelihood that some patients exposed chronically to antipsychotics will develop tardive dyskinesia, it is advised that allpatients in whom chronic use is contemplated be given, if possible, full information about this risk.

Usage In Pregnancy

The safety of this drug in pregnancy has not been established; hence, it should be given only when the anticipated benefits to be derived from treatment exceed the possible risks to mother and fetus.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

ADVERSE REACTIONS

Drowsiness and hypotension were the most prevalent side effects encountered. Side effects tended to reach their maximum level of severity early with the exception of a few (rigidity and motoric effects) which occurred later in therapy.

With the exceptions of tremor and rigidity, adverse reactions were generally found among those patients who received relatively high doses early in treatment. Clinical data showed no tendency for the investigators to terminate treatment because of side effects.

Central Nervous System: Drowsiness, Parkinson's syndrome, dizziness, weakness, tremor, restlessness, ataxia, dystonia, rigidity, slurring, akathisia, motoric reactions (opisthotonos) have been reported.

Autonomic Nervous System: Dry mouth, nausea and vomiting, fainting, stuffy nose, photophobia, constipation and blurred vision have occurred in some instances.

Genitourinary System: Inhibition of ejaculation, impotence, enuresis, incontinence, and priapism have been reported.

Skin: Itching, rash, hypertrophic papillae of the tongue and angioneurotic edema have been reported.

Cardiovascular System: Serentil® (mesoridazine besylate) produces a dose related prolongation of the QTc interval, which is associated with the ability to cause torsade de pointes-type arrhythmias, a potentially fatal polymorphic ventricular tachycardia, and sudden death (see WARNINGS). Ventricular arrhythmias and death have been reported in association with Serentil overdosage. A causal relationship between these events and Serentil therapy has not been established but, given the ability of Serentil to prolong the QTc interval, such a relationship is possible. Other ECG changes have been reported (see Phenothiazine Derivatives: Cardiovascular Effects).

Phenothiazine Derivatives

It should be noted that efficacy, indications and untoward effects have varied with the different phenothiazines. The physician should be aware that the following have occurred with one or more phenothiazines and should be considered whenever one of these drugs is used.

Autonomic Reactions: Miosis, obstipation, anorexia, paralytic ileus.

Cutaneous Reactions: Erythema, exfoliative dermatitis, contact dermatitis.

Blood Dyscrasias: Agranulocytosis, leukopenia, eosinophilia, thrombocytopenia, anemia, aplastic anemia, pancytopenia.

Allergic Reactions: Fever, laryngeal edema, angioneurotic edema, asthma.

Hepatotoxicity: Jaundice, biliary stasis.

Cardiovascular Effects: Changes in the terminal portion of the electrocardiogram, to include prolongation of the QT interval, depression and inversion of the T wave, and the appearance of a wave tentatively identified as a bifid T wave or a U wave have been observed in patients receiving phenothiazines, including Serentil. To date, these appear to be due to altered repolarization, not related to myocardial damage, and appear to be reversible. Nonetheless, significant prolongation of the QT interval has been associated with serious ventricular arrhythmias and sudden death (see WARNINGS). Hypotension, rarely resulting in cardiac arrest, has been reported.

Extrapyramidal Symptoms: Akathisia, agitation, motor restlessness, dystonic reactions, trismus, torticollis, opisthotonos, oculogyric crises, tremor, muscular rigidity, akinesia.

Tardive Dyskinesia: Chronic use of antipsychotic may be associated with the development of tardive dyskinesia. The salient features of this syndrome are described in the WARNINGS section and below.

The syndrome is characterized by involuntary choreoathetoid movements which variously involve the tongue, face, mouth, lips, or jaw (e.g., protrusion of the tongue, puffing of cheeks, puckering of the mouth, chewing movements), trunk and extremities. The severity of the syndrome and the degree of impairment produced vary widely.

The syndrome may become clinically recognizable either during treatment upon dosage reduction, or upon withdrawal of treatment. Movements may decrease in intensity and may disappear altogether if further treatment with antipsychotic is withheld. It is generally believed that reversibility is more likely after short rather than long-term antipsychotic exposure. Consequently, early detection of tardive dyskinesia is important. To increase the likelihood of detecting the syndrome at the earliest possible time, the dosage of antipsychotic drug should be reduced periodically (if clinically possible) and the patient observed for signs of the disorder. This maneuver is critical, for antipsychotic drugs may mask the signs of the syndrome.

Endocrine Disturbances: Menstrual irregularities, altered libido, gynecomastia, lactation, weight gain, edema. False positive pregnancy tests have been reported.

Urinary Disturbances: Retention, incontinence.

Others: Hyperpyrexia. Behavioral effects suggestive of a paradoxical reaction have been reported. These include excitement, bizarre dreams, aggravation of psychoses and toxic

confusional states. More recently a peculiar skin-eye syndrome has been recognized as a side effect following long-term treatment with phenothiazines. This reaction is marked by progressive pigmentation of areas of the skin or conjunctiva and/or accompanied by discoloration of the exposed sclera and cornea. Opacities of the anterior lens and cornea described as irregular or stellate in shape have also been reported. Systemic lupus erythematosus-like syndrome.

OVERDOSAGE

Symptoms of Acute Overdosage

Drowsiness, confusion, disorientation, agitation, coma, death.

Dryness of mouth, edema of glottis, laryngeal spasms, nasal congestion, blurred vision, vomiting.

Hyperpyrexia, dilated pupils, muscle rigidity, hyperactive reflexes, areflexia.

Stupor, and CNS depression or stimulation with convulsions followed by respiratory depression.

Cardiac abnormalities, including QRS changes, tachycardia, hypotension, bilateral bundle branch block, ventricular fibrillation, shock, cardiac arrest and congestive heart failure.

Treatment of Acute Overdosage

An airway must be established and maintained. Adequate oxygenation and ventilation must be ensured.

Cardiovascular monitoring should commence immediately and should include continuous electrocardiographic monitoring to detect possible arrhythmias. Treatment may include one or more of the following therapeutic interventions: correction of electrolyte abnormalities and acid-base balance, lidocaine, phenytoin, isoproterenol, ventricular pacing, and defibrillation. Disopyramide, procainamide, and quinidine may produce additive QT-prolonging effects when administered to patients with acute overdosage of Serentil® (mesoridazine besylate) and should be avoided (see CONTRAINDICATIONS, WARNINGS, and PRECAUTIONS). Caution must be exercised when administering lidocaine, as it may increase the risk of developing seizures.

Treatment of hypotension may require intravenous fluids and vasopressors. Phenylephrine, levarterenol, or metaraminol are the appropriate pressor agents for use in the management of refractory hypotension. The potent α-adrenergic blocking properties of the phenothiazines makes the use of vasopressors with mixed α and ß adrenergic agonist properties inappropriate, including epinephrine and dopamine. Paradoxical vasodilation may result. In addition, it is reasonable to expect that the α-adrenergic blocking properties of bretylium might be additive to those of Serentil, resulting in problematic hypotension.

In managing overdosage, the physician should always consider the possibility of multiple drug involvement. Gastric lavage and repeated doses of activated charcoal should be considered. Induction of emesis is less preferable to gastric lavage because of the risk of

dystonia and the potential for aspiration of vomitus. Emesis should not be induced in patients expected to deteriorate rapidly or in those with impaired consciousness.

No specific antidote is known.

Acute extrapyramidal symptoms may be treated with diphenhydramine hydrochloride or benztropine mesylate.

Avoid the use of barbiturates when treating seizures, as they may potentiate phenothiazine-induced respiratory depression.

Forced diuresis, hemoperfusion, hemodialysis, and manipulation of urine pH are of unlikely benefit in the treatment of phenothiazine overdose due to their large volume of distribution and extensive plasma protein binding.

Up-to-date information about the treatment of overdose can often be obtained from a certified Regional Poison Control Center. Telephone numbers of certified Regional Poison Control Centers are listed in the Physicians'Desk Reference®*.

DOSAGE AND ADMINISTRATION

Since Serentil® (mesoridazine besylate) is associated with a dose-related prolongation of the QTc interval, which is a potentially life-threatening event its use should be reserved for schizophrenia patients who fail to respond adequately to treatment with other antipsychotic drugs (see INDICATIONS and WARNINGS).

The dosage of Serentil, as with most medications, should be adjusted to the needs of the individual. The lowest effective dosage should always be used. When maximum response is achieved, dosage may be reduced gradually to a maintenance dose.

Tablets and Oral Solution

For most patients, regardless of severity, a starting dose of 50 mg three times a day is recommended. The usual optimum total daily dose range is 100-400 mg per day.

Injectable Form

In those situations in which an intramuscular form of medication is indicated, Serentil injectable is available. For most patients, a starting dose of 25 mg is recommended. The dose may be repeated in 30 to 60 minutes, if necessary. The usual optimum total daily dose range is 25-200 mg per day.

HOW SUPPLIED

Tablets mesoridazine (as the besylate).

Bottles of 100.

10 mg..... .... NDC 0597-0020-01

25 mg..... .... NDC 0597-0021-01

50 mg..... .... NDC 0597-0022-01

100 mg..... .... NDC 0597-0023-01

Ampuls 1 mL [25 mg mesoridazine (as the besylate)].

Boxes of 20 .... NDC 0597-0027-02

Concentrate Contains 25 mg mesoridazine (as the besylate) per mL, alcohol, USP, 0.61% by volume. Immediate containers: Amber glass bottles of 4 fl oz (118 mL) packaged in cartons of 12 bottles, with an accompanying dropper graduated to deliver 10 mg, 25 mg, and 50 mg of mesoridazine (as the besylate)..... ..... NDC 0597-0025-04

STORAGE

Tablets: **Store at 25°C (77°F); excursions permitted to 15°C-30°C (59°F-86°F). [See USP Controlled Room Temperature] Dispense in a tight container (USP)**

Injection: **Store at 25°C (77°F); excursions permitted to 15°C-30°C (59°F-86°F). [See USP Controlled Room Temperature] Dispense in a tight container (USP)**

Oral solution: Store below 77°F (25°C); protect from light; dispense in amber glass bottles only.

The concentrate may be diluted with distilled water, orange juice or grape juice. Each dose should be diluted just prior to administration. Preparation and storage of bulk dilutions is not recommended.

Additional information available to physicians.

PHARMACOLOGY

Pharmacological studies in laboratory animals have established that Serentil® (mesoridazine besylate) has a spectrum of pharmacodynamic actions typical of an antipsychotic. In common with other antipsychotics it inhibits spontaneous motor activity in mice, prolongs thiopental and hexobarbital sleeping time in mice and produces spindles and block of arousal reaction in the EEG of rabbits. It is effective in blocking spinal reflexes in the cat and antagonizes d-amphetamine excitation and toxicity in grouped mice. It shows a moderate adrenergic blocking activity in vitro and in vivo and antagonizes 5-hydroxytryptamine in vivo. Intravenously administered, it lowers the blood pressure of anesthetized dogs. It has a weak antiacetylcholine effect in vitro.

The most outstanding activity of Serentil is seen in tests developed to investigate antiemotive activity of drugs. Such tests are those in which the rat reacts to acute or chronic stress by increased defecation (emetogenic defecation) or tests in which "emotional mydriasis" is elicited in the mouse by an electric shock. In both of these tests Serentil is effective in reducing emotive reactions. Its ED_{50} in inhibiting emetogenic defecation in the rat is 0.053 mg/kg (subcutaneous administration). Serentil has a potent antiemetic action. The intravenous ED_{50} against apomorphine-induced emesis in the dog is 0.64 mg/kg. Serentil, in common with other phenothiazines, demonstrates antiarrhythmic activity in anesthetized dogs.

Metabolic studies in the dog and rabbit with tritium labeled mesoridazine demonstrate that the compound is well absorbed from the gastrointestinal tract. The biological half life of Serentil in these studies appears to be somewhere between 24 to 48 hours. Although significant urinary excretion was observed following the administration of Serentil, these studies also suggest that biliary excretion is an important excretion route for mesoridazine and/or its metabolites.

Toxicity Studies

Acute LD_{50} (mg/kg):

Route	Mouse	Rat	Rabbit	Dog
Oral	560±62.5	644±48	MLD=800	MLD=800
I.M.	--	509M 584F	405	--
I.V.	26±0.08	--	--	--

Chronic toxicity studies were conducted in rats and dogs. Rats were administered Serentil orally seven days per week for a period of seventeen months in doses up to 160 mg/kg per day. Dogs were administered Serentil orally seven days per week for a period of thirteen months. The daily dosage of the drug was increased during the period of this test such that the "top-dose" group received a daily dose of 120 mg/kg of mesoridazine for the last month of the study.

Untoward effects which occurred upon chronic administration of high dose-levels included:

Rats

Reduction of food intake, slowed weight gain, morphological changes in pituitary supported endocrine organs, and melanin-like pigment deposition in renal tissues.

Dogs

Emesis, muscle tremors, decreased food intake and death associated with aspiration of oral-gastric contents into the respiratory system.

Increased intrauterine resorptions were seen with Serentil in rats at 70 mg/kg and in rabbits at 125 mg/kg but not at 60 and 100 mg/kg, respectively. No drug related teratology was suggested by these reproductive studies.

Local irritation from the intramuscular injection of Serentil was of the same order of magnitude as with other phenothiazines.

* Trademark of Medical Economics Company, Inc.

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Boehringer Ingelheim

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Novartis Pharmaceuticals Canada, Inc.
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