DESCRIPTION
Isosterol mononotrate (SMN), an organic nitrile and the major biologically active constituent of isosterol anthracene (ISA), is a vasodilator with effects on both arteries and veins.

Each tablet, for oral administration, contains 50 mg, 60 mg or 120 mg isosterol mononitrate in an enteric-coated form. In addition, each tablet contains the following inactive ingredients: colloidal silicon dioxide, hydroxypropyl cellulose, hypromellose, lactose monohydrate, magnesium stearate, microcrystalline cellulose and talc. The molecular formula of SMN is C21H19NO4 and the molecular weight is 385.34. Its chemical name for 1,4-endo-3-tetrahydro-5-thiophenyl-4-quinazolinone-3-thione.

SMN is a white, crystalline, odorless compound which is stable in air and in solution, has a melting point of about 40°C, and an optical rotation of 41° (2°C in water, 20°C).

Isosterol mononitrate is freely soluble in water, an alcohol, methanol, ethanol, chloroform, ethyl acetate and dichloroacetic acid.

Clinical Pharmacology and Mechanism of Action
The Isosteol Monoborate Extended-Release Tablet, USP is an oral extended-release formulation of SMN which has been designed to provide a steady, constant, and predictable release of isosteol dye distal to the clinical activity of the distal is not attributable to the mononitrate.

The pharmacological action of SMN and all organic nitriles in general is reactivity of vascular smooth muscle, producing dilatation (dilatation is usually the latter). Dilatation of the walls promotes peripheral pooling of blood, decreases venous return to the heart, thereby reducing left ventricular and diastolic pressure and pulmonary arterial wedge pressure (neaia). Alpha-2 adrenal blockade reduces the systemic vascular resistance, systemic arterial pressure, and cardiac output (cardiac output decrease in arterioles). Drugs of this class also reduce heart rate and cardiac output.

The influence of SMN on the vital activity of ISA in single-dose administration of SMN as an oral solution at various concentrations of ISA in vitro.

The following tables summarize key pharmacokinetic parameters of SMN after single- and multiple-dose administration of SMN as an oral solution at various concentrations of ISA in vitro.

Food Effects
The influence of food on the bioavailability of ISA after single-dose administration of isosteol mononitrate and isosteol mononitrate tablets 60 mg and 120 mg was evaluated in 12 healthy subjects randomized into two different studies involving at least 6 subjects each. The difference in bioavailability between the two groups was about 30% as measured by the percentage decrease in bioavailability.

Pharmacodynamics and Metabolism
After oral administration of SMN as a solution in immediate-release tablets, the plasma concentrations of SMN are achieved in 30 to 60 minutes, with an absolute bioavailability of approximately 100%. After oral administration of SMN in isotonic enteric-coated tablets, the plasma concentrations of SMN are achieved in 30 to 60 minutes, with a volume of distribution of approximately 6.64-L/kg. Isosteol mononitrate is approximately 5% bound to human plasma proteins and is distributed into blood cells and saliva. Isosteol mononitrate is primarily metabolized by the liver to its biologically active 5-carboxylic acid metabolite. These metabolites are primarily eliminated in the urine. At least six different compounds have been identified in urine, with about 2% of dose excreted as the unchanged drug and about 5% of the metabolites. The metabolites are not pharmacologically active.

The disposition of SMN in patients with various ages of renal insufficiency, liver disease, or cardiac dysfunction was not evaluated and found to be similar to that observed in healthy volunteers. The elimination half-life of SMN was not significantly changed in patients with chronic renal failure as compared to normal subjects.

The pharmacokinetics and bioavailability of isosteol mononitrate tablets have been evaluated in patients and patients following single- and multiple-dose administration. Data from these studies suggest that the pharmacokinetics of SMN administered as isosteol mononitrate tablets are similar in patients to those observed in normal patients. There is no significant difference in the pharmacokinetics of SMN between elderly (65 years) and younger individuals (45-49 years) for the isosteol mononitrate

undertaken-release 60 mg dose. The administration of isosteol mononitrate extended-release 130 mg (2 x 65 mg tablets) every 24 hours for 7 days produced no significant changes in mean arterial pressure or mean heart rate compared to baseline.

WESTERN DIET: In a study of 12 healthy male volunteers who received 120 mg (2 x 60 mg) extended-release isosteol mononitrate every 24 hours, the results of the study showed no significant differences in any of the pharmacokinetic variables of SMN between elderly (65 years) and younger individuals (45-49 years) for the isosteol mononitrate extended-release 60 mg dose. The administration of isosteol mononitrate extended-release 130 mg (2 x 65 mg tablets) every 24 hours for 7 days produced no significant changes in mean arterial pressure or mean heart rate compared to baseline.

PREREQUISITES
General
Nitrates are not indicated for patients with an allergy to isosteol mononitrate or isosteol mononitrate extended-release tablets. In addition, nitrates may be contraindicated in patients with a history of hypersensitivity to organic nitrates.

Nitrates may also be contraindicated in patients with a history of hypotension, hyperplasia of the aorta, or severe aortic stenosis.

Mesna hydrochloride may antagonize the effects of organic nitrates and is not recommended for use in patients with a history of mesna hydrochloride intolerance.

Mesna hydrochloride may also be contraindicated in patients with a history of urea hydrochloride intolerance.

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Shire and Aventis Pharmaceuticals: Accru, head搬家 abnormal, increased sweating, pruritus, rash, skin nodules.

Neurological System Disorders: Dizziness, restless calciulus, urinary tract infection.

Muscular (Extracranial) Disorders: Rhabdomyolysis, arrhythmia, hyperkalemia, bone malacia.

Intestinal: Constipation, hemorrhoids, vision abnormal, diarrhea.

In addition, the following paroxysmal adverse event has been reported during the marketing of losoide monotherapy: syncope.

OVERDOSE

Hemodynamic Effects

The lack of evidence for losoide monotherapy overdose is generally the result of losoide monotherapy's capacity to induce vasodilation, venous pooling, without cardiac output, and hypotension. These hemodynamic changes may have greater manifestations, including increased intracranial pressure, with any or all of persistent hypertension, headache, confusion, and moderate fever, vomiting, decreased visual acuity, nausea and vomiting (possibly with colic and even bloody diarrhea), syncope (especially in the upright posture), anorexia, nausea, and vomiting of other gastrointestinal effects: diaphoresis, diarrhea, nausea, vomiting, and diarrhea. Laboratory determinations of plasma levels of losoide monotherapy and its metabolites are not widely available, and such determinations have not established in the management of losoide monotherapy overdose.

There are no data suggesting what dose of losoide monotherapy is likely to be lethal in humans. In general, less than 30 mg/kg per day, in adults, is significant to high at doses of 2500 mg/kg and 3000 mg/kg, respectively. No deaths are available to suggest physiological consequences (e.g., neurotoxicity) to losoide monotherapy overdose. Multiple deaths have been attributed to losoide monotherapy overdose; however, there is no evidence that losoide monotherapy overdose is the result of vasodilation and arterial hypotension. Laboratory tests in this situation should be directed toward an increase in central blood volume. Prolonged elevation of the patient's body may be significant, but intravenous fluid's of normal saline or dextrose may also be necessary.

The use of epinephrine or other arterial vasopressors in this setting is likely to be of no harm but good.

In patients with renal failure or congestive heart failure, therapy resulting in central volume expansion is not without risk. Treatment of losoide monotherapy overdose in these patients may be futile and ineffective, and intensive monitoring may be required.

Methemoglobinemia

Methemoglobinemia has been reported in patients receiving other organics, and it is probably also seen as a side effect of losoide monotherapy. However, these values are not available to suggest physiological consequences (e.g., neurotoxicity) to losoide monotherapy overdose. Multiple deaths have been attributed to losoide monotherapy overdose; however, there is no evidence that losoide monotherapy overdose is the result of vasodilation and arterial hypotension. Laboratory tests in this situation should be directed toward an increase in central blood volume. Prolonged elevation of the patient's body may be significant, but intravenous fluid's of normal saline or dextrose may also be necessary.

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