RELISPA (Drotaverine HCl)
RELISPA FORTE (Drotaverine HCl)

40 mg & 80 mg

Tablet & Injection

COMPOSITION

Tablets

Each Relispa tablet contains:
Drotaverine hydrochloride.... 40 mg

Each Relispa Forte tablet contains:
Drotaverine hydrochloride…. 80 mg

Injection

Each Relispa 2 ml ampoule contains:
Drotaverine hydrochloride……...40mg

Each Relispa Forte 4 ml ampoule contains:
Drotaverine hydrochloride…….80 mg

THERAPEUTIC INDICATIONS

Smooth muscle spasms associated with gallbladder and biliary tract disease: cholelithiasis, cholangiolithiasis, cholecystitis, cholangitis, peri cholecystitis, papillitis (inflammation of the papilla).

Renal and urinary smooth muscle spasms: nephrolithiasis, ureterolithiasis, pyelitis, cystitis, vesical tenesmus.

Adjuvant treatment for:

Spastic conditions of the gastrointestinal tract: gastric and duodenal ulcers, gastritis, cardiac and pyloric spasms, enteritis, colitis, spastic colitis with constipation and flatulence in irritable bowel syndrome.

Tension headache

Gynecological disorders - dysmenorrhea.

DOSAGE AND ADMINISTRATION

Adults

Tablet

The usual daily dose is 120 ─ 240 mg orally in 2 ─ 3 divided doses.

Injection

The usual average daily dose is 40-240 mg (in 1-3 divided doses)

Acute stone colic (renal and / or biliary):40-80mg Drotaverine hydrochloride was intravenously slowly injected (about 30 seconds) or non-narcotic analgesic drugs.

Abdominal spastic pain: 40-80mg Drotaverine hydrochloride intramuscularly, when necessary, can be repeated up to 3 times daily.

Pediatric population

The use of drotaverine in children has not been evaluated in clinical studies. This medicine is contraindicated in children less than 1 year of age.

CONTRAINDICATIONS

Hypersensitivity to the active substance or to any of the excipients

Severe renal or hepatic failure.

Severe heart failure (low heart rate syndrome).

Children under 1 year.

SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Caution should be exercised when administering the drug for hypotension.

Tablet contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

In the case of intravenous administration, the patient must be in a supine position due to the risk of collapse.

Caution should be exercised when injecting drotaverine into pregnant women.

Injection contains sodium disulphite, which may rarely cause severe hypersensitivity reactions (including anaphylactic shock) and bronchospasm in sensitive people - especially if they have a history of asthma or allergies. If the patient is allergic to disulphites, drotaverine injection must not be administered.

This medicine may be harmful to those who suffer from alcoholism. It must be taken into account in breast-feeding and pregnant women, children and high-risk groups such as patients with liver disease or epilepsy.

Pediatric population

The use of drotaverine in children has not been evaluated in clinical studies. This medicine is contraindicated in children less than 1 year of age

DRUG INTERACTIONS

Phosphodiesterase inhibitors, e.g. papaverine, reduce the antiparkinsonian effect of levodopa. Drotaverine may reduce the antiparkinsonian effect of levodopa, thus worsening tremor and rigidity.

FERTILITY, PREGNANCY AND LACTATION

Pregnancy

Only limited data on exposed pregnancies are available. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy or embryonal / fetal development. Nevertheless, caution should be exercised when prescribing to pregnant women.

Breast feeding

The excretion of drotaverine in milk has not been studied in animals. Therefore, the use of drotaverine during breast-feeding is not recommended.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Oral administration of the recommended therapeutic doses has not been shown to affect the ability to drive or use machines.

Following parenteral administration, especially intravenous administration, it is not recommended to drive or use machines within 1 hour of administration.

ADVERSE DRUG REACTIONS

The following side effects are classified according to system organ class and are based on frequency:

very common (≥ 1/10), uncommon (≥ 1/100 to <1/10), uncommon (≥ 1 / 1,000 to <1/100), rare (≥ 1 / 10,000 to <1 / 1,000), very rare (<1 / 10,000), unknown (from available data).

Gastrointestinal disorders

Rare: nausea, constipation.

Nervous system disorders

Rare: headache, vertigo, insomnia.

Heart and heart disorders

Rare: palpitations, hypotension.

Immune system disorders

Rare: allergic reactions (angioedema, urticaria, rash, pruritus).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after marketing authorization is important. It allows continuous monitoring of the benefit-risk balance of the drug. Health professionals are required to report any suspected adverse reactions at pv@searlecompany.com

OVERDOSE

symptoms

Drotaverine overdose has been associated with heart rhythm and conduction disturbances, including complete blockage of the Tawar arms and cardiac arrest, which can be fatal.

treatment

In the event of an overdose, the patient should be closely monitored. Treatment should be symptomatic and supportive. Suggested measures include emesis and/or gastric lavage.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties

Pharmacotherapeutic group: Drugs for functional gastrointestinal disorders; papaverine and derivatives; ATC code: A03AD02.

Mechanism of action

Drotaverine is an isoquinoline derivative whose significant antispasmodic effect is inhibition of phosphodiesterase IV (PDE IV). PDE IV is the enzyme responsible for the hydrolysis of cAMP to AMP. Inhibition of this enzyme leads to an increased concentration of cAMP, triggering a whole cascade of mechanisms as described below. High concentrations of cAMP activate cAMP-dependent protein kinase phosphorylating myosin light chain kinase (MLCK). Phosphorylation of MLCK leads to a decrease in its affinity for the Ca^{2+} -calmodulin complex and the inactive form of MLCK keeps the muscle in a state of relaxation. cAMP also affects the concentration of cytoplasmic $Ca^{2+}$by stimulating the transport of calcium ions into the extracellular space and into the sarcoplasmic reticulum. This decrease in the concentration of calcium ions in the cytoplasm by cAMP explains its antagonistic effects on calcium.

In vitro, it inhibits drotaverine PDE IV but not the PDE III and PDE V isoenzymes. PDE IV appears to be an enzyme responsible for reducing smooth muscle contractility, suggesting that selective PDE IV inhibitors may be effective in the treatment of hypermotility and many diseases associated with spastic conditions. gastrointestinal tract.

The enzyme responsible for the hydrolysis of cAMP in cardiovascular muscle is primarily PDE III, which explains why drotaverine is an effective antispasmodic without a therapeutic effect on the cardiovascular system and serious cardiovascular side effects.

Pharmacokinetic properties

Absorption

In humans, peak plasma concentrations of drotaverine are reached after approximately 45-60 minutes, indicating rapid absorption of drotaverine. A dose of 37 mg of drotaverine was administered orally in 20 ml of aqueous solution. Based on radioactivity measurements, almost complete absorption was found. The maximum plasma concentration is reached 45 ─ 90 min after administration, the absorption half-life is 12 min. Following oral administration of 80 mg drotaverine hydrochloride, peak plasma concentrations (136 ─ 320 ng / ml) are reached after 2 h.

Distribution

Drotaverine and / or its metabolites hardly cross the placental barrier.

In vitro , drotaverine is highly bound (95-98%) to plasma proteins, primarily albumin, γ- and β-globulins, and α- (HDL) -lipoproteins.

Biotransformation

Drotaverine is almost completely metabolized by O-deethylation to monophenolic compounds. These metabolites are rapidly conjugated to glucuronic acid. The major metabolite is 4'-deethyldrotaverine. 6'-deethyldrotaverine and 4'-deethyldrotaverine were also found.

Drotaverine undergoes hepatic first-pass metabolism in humans and only 65% of the dose enters the systemic circulation unchanged.

A 2-compartment model was used to determine pharmacokinetic parameters in humans.

Elimination

The terminal elimination half-life of drotaverine is 16 ─ 22 hours.

During 168 hours after i. in. approximately 41-45% is excreted in the urine, 31-36% in the feces. Another study found that 54-73% of drotaverine was excreted in the urine and only 10-32% in the feces.

PRECLINICAL SAFETY DATA

Preclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, genotoxicity and toxicity to reproduction:

Based on *in vitro* and in *vivo studies*, drotaverine did not induce a delay in ventricular repolarization.

Drotaverine was deprived of genotoxic potential in a range of *in vitro* and in *vivo* mutagenicity studies, i. j. in the Ames test, in the mouse lymphoma test and in the rat micronucleus test.

Drotaverine does not affect rat fertility or embryonal / fetal development in rats and rabbits.

Acute toxicity

The results obtained in the experiments on albino mice are summarized in the following table:

compound	LD_{50} (mg / kg)		
papaverine	31.0	290.0	> 2,000
perparín	27.0	> 1,000	> 3,000
drotaverine (isodihydroperparin)	19.0	95.0	1,000

The table shows that the largest difference between the acute toxicity of the monitored isoquinoline derivatives is in the case of subcutaneous administration, this is probably due to the easier absorption of hydrated derivatives.

Chronic toxicity and teratogenicity

Drotaverine was administered orally at doses of 8-16 mg / kg for four months to dogs and rats, the animals were each divided into two groups. None of the animals showed any abnormalities during the study. Histological evaluation at the end of the study showed no evidence of toxicity. When drotaverine was administered to pregnant female rats, they gave birth to normal pups at the usual time.

In another study, drotaverine was administered orally in 6 repeated doses of 10 mg / kg / day between days 7 and 12 in pregnant female F1-generation inbred *R-Amsterdam* rats without adverse effects on the fetus; no case of death or malformation was identified.

These data suggest that drotaverine has no teratogenic or embryotoxic effects.

Drotaverine has also been studied for embryotoxicity and teratogenicity in albino *Wistar rats* and guinea pigs. No differences were found compared to the control group of animals not given drotaverine. The number of births remained normal and no malformations were found; these data are also valid for the second generation of these experimental animals and therefore drotaverine can be considered safe in terms of embryotoxicity and teratogenicity in animals.

Other results obtained in rats are also in agreement with the above data.

PRESENTATION

Tablets

Relispa 40 mg tablets are available as a Box of 20 tablets

Relispa Forte 80 mg tablets are available as a Boxes of 20 tablets

Injection

Relispa 40 mg injection is available as a Box of 25 ampoules

Relispa Forte 80 mg injection is available as a Box of 10 ampoules

INSTRUCTIONS

To be sold on prescription of a registered medical practitioner only.

Keep out of the reach of children.

Store below 30°C.

Should not be used if solution contains undissolved particles or clouds.

REGISTRATION NUMBER

Relispa 40 mg Tablets: 039262

Relispa Forte 80 mg Tablets: 039263

Relispa 2 ml ampoule 40mg/2ml: 053344

Relispa Forte 4 ml ampoule 80mg/4ml: 058489

Manufacturing License No: 000016

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION

Mfg. Searle Specs.

Manufactured by:

The Searle Company Limited

F-319, S.I.T.E., Karachi-Pakistan.

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