LOMOTIL
(Diphenoxylate Hydrochloride BP and Atropine Sulphate Ph. Eur.)

2.5 mg & 0.025 mg

Tablets

COMPOSITION

Each tablet for oral administration contains:
Diphenoxylate Hydrochloride…… BP 2.5 mg
Atropine Sulfate Ph. Eur…… 0.025 mg

THERAPEUTIC INDICATIONS

Adults

Lomotil is indicated as adjunctive therapy in the management of diarrhea in patients 13 years of age and older.

Pediatric use

The safety and effectiveness of Lomotil have been established in pediatric patients 13 years of age and older as adjunctive therapy in the management of diarrhea. The safety and effectiveness of Lomotil have not been established in pediatric patients less than 13 years of age.
Lomotil is contraindicated in pediatric patients less than 6 years of age due to the risks of severe respiratory depression and coma, possibly resulting in permanent brain damage or death.
Lomotil has caused atropinism, particularly in pediatric patients with Down's syndrome

DOSAGE AND ADMINISTRATION

Management of Diarrhea in Patients 13 Years of Age and Older
Lomotil is recommended as adjunctive therapy for the management of diarrhea in patients 13 years of age and older. Consider the nutritional status and degree of dehydration in patients prior to initiating therapy with Lomotil. The use of Lomotil should be accompanied by appropriate fluid and electrolyte therapy, when indicated. If severe dehydration or electrolyte imbalance is present, do not administer Lomotil until appropriate corrective therapy has been indicated.

Initial and Maximum Recommended Dosage in Patients 13 Years of Age and Older
The initial adult dosage is 2 Lomotil tablets four times daily (maximum total daily dose of 20 mg per day of diphenoxylate hydrochloride). Most patients will require this dosage until initial control of diarrhea has been achieved. Clinical improvement of acute diarrhea is usually observed within 48 hours.

Dosage after Initial Control of Diarrhea
After initial control has been achieved, the Lomotil dosage may be reduced to meet individual requirements. Control may often be maintained with as little as two Lomotil tablets daily.

Duration of Treatment
If clinical improvement of chronic diarrhea after treatment with the maximum recommended daily dosage is not observed within 10 days, discontinue Lomotil as symptoms are unlikely to be controlled by further administration

Method of Administration

Oral.

CONTRAINDICATIONS

Lomotil is contraindicated in-patients with a known hypersensitivity to diphenoxylate hydrochloride or atropine, inpatients with jaundice, intestinal obstruction, acute ulcerative colitis, myasthenia gravis, pyloric stenosis, paralytic ileus, prostatic enlargement, in the treatment of diarrhoea associated with pseudomembranous enterocolitis and in patients with a raised intracranial pressure, and patients with head injury.

SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Respiratory and/or CNS Depression in Pediatric Patients Less Than 6 Years of Age

Cases of severe respiratory depression and coma, leading to permanent brain damage or death have been reported in patients less than 6 years of age who received Lomotil. Lomotil is contraindicated in patients less than 6 years of age due to these risks.

Anticholinergic and Opioid-Toxicities

Toxicities associated with the atropine and diphenoxylate components of Lomotil have been reported. The initial presenting symptoms may be delayed by up to 30 hours due to prolonged gastric emptying time induced by diphenoxylate hydrochloride. Clinical presentations vary in terms of which toxicity (anticholinergic vs. opioid) will present first or predominate; non-specific findings have been reported and include symptoms such as drowsiness.

Dehydration and Electrolyte Imbalance

The use of Lomotil should be accompanied by appropriate fluid and electrolyte therapy, when indicated. If severe dehydration or electrolyte imbalance is present, Lomotil should be withheld until appropriate corrective therapy has been initiated. Drug-induced inhibition of peristalsis may result in fluid retention in the intestine, which may further aggravate dehydration and electrolyte imbalance.

Gastrointestinal Complications in Patients with Infectious Diarrhea

Lomotil is contraindicated in patients with diarrhea associated with organisms that penetrate the GI mucosa (toxigenic *E. coli, Salmonella, Shigella*), and pseudomembranous enterocolitis (*Clostridium difficile*) associated with broad-spectrum antibiotics. Antiperistaltic agents, including Lomotil, slow gastrointestinal motility and may enhance bacterial overgrowth and the release of bacterial exotoxins. Lomotil has been reported to result in serious GI complications in patients with infectious diarrhea, including sepsis, prolonged and/or worsened diarrhea. Prolonged fever and the delay in the resolution of stool pathogens were reported in study of Shigellosis in adults who used Lomotil vs. placebo.

Toxic Megacolon in Patients with Acute Ulcerative Colitis

In some patients with acute ulcerative colitis, agents that inhibit intestinal motility or prolong intestinal transit time have been reported to induce toxic megacolon. Consequently, patients with acute ulcerative colitis should be carefully observed and Lomotil therapy should be discontinued promptly if abdominal distention occurs or if other untoward symptoms develop.

Interaction with Meperidine Hydrocholoride

Since the chemical structure of diphenoxylate hydrochloride is similar to that of meperidine hydrochloride, the concurrent use of Lomotil with monoamine oxidase (MAO) inhibitors may, in theory, precipitate hypertensive crisis.

Hepatorenal Disease

Lomotil should be used with extreme caution in patients with advanced hepatorenal disease and in all patients with abnormal liver function since hepatic coma may be precipitated.

Interaction with CNS Depressants

Diphenoxylate hydrochloride may potentiate the action of other drugs that cause dizziness or drowsiness, including barbiturates, benzodiazepines and other sedatives/hypnotics, anxiolytics, and tranquilizers, muscle relaxants, general anesthetics, antipsychotics, other opioids, and alcohol. Therefore, the patient should be closely observed when any of these are used concomitantly.

DRUG INTERACTIONS

Diphenoxylate hydrochloride may potentiate the action of narcotic or sedative drugs such as barbiturates, tranquillisers and alcohol.

The following potential interactions have to be considered in the use of Lomotil Tablets: -

Opiod analgesics antagonises the effects of Domperidone, Metoclopramide, Cisapride.

Antimuscarinics such as atropine antagonise the muscarinic effects of Bethanecol/Carbachol, Galantamine, Donepezil, Neostigmine/pyridostigmine, and Pilcarpine.

Memantine possibly enhances the effects of antimuscarinics.

Absorption of Levodopa possibly reduced by antimuscarinics. Antimuscarinics reduces the absorption of Ketoconazole.

The anticholinergic effects of this product may be enhanced by the concomitant administration of Amantadine, Anthihistamines (sedative and non-sedative), Clozapine, Disopyramide, Fluspiriline, Loxapine, MAOI's, Nefopam, Olanzapine, Phenothiazines, Quantiapine, Remoxipride, Terfenadine, Tricyclic antidepressasnts, and Zotepine.

Dry mouth prevents the dissolution of sublingual nitrate tablets, such as glyceryl trinitrate

EFFECTS ON ABILITY TO DRIVE

Some of the undesirable effects such as sedation, drowsiness or dizziness may affect the ability to drive or operate machines. If affected, patients should be advised not to drive or operate machinery.

FERTILITY, PREGNANCY AND LACTATION

Pregnancy

Safety of Lomotil in human pregnancy has not been established, although animal teratology and reproduction studies have demonstrated no adverse effects. Lomotil should not be used in pregnancy unless considered essential by the physician.

Lactation

Diphenoxylate hydrochloride and atropine sulphate may be excreted in human milk. Lomotil should not be used in nursing mothers.

ADVERSE DRUG REACTIONS

Adverse reactions reported included:

Central nervous: Malaise/lethargy/sedation/somnolence, confusion, dizziness, restlessness, depression, euphoria, hallucinations, headache and giddiness.

General disorders: Fever Atropine effects such as flushing and hypothermia may occur. Cardiac disorders: The atropine side effects of Lomotil Tablets include cardiac irregularities such as arrhythmias, bradycardia, tachycardia, and palpitations.

Allergic: Anaphylaxis, angioedema, urticaria and pruritus.

Gastrointestinal system: Paralytic ileus, toxic megacolon, gastrointestinal intolerance such as nausea and vomiting, anorexia, constipation, abdominal discomfort and dry mouth.

Skin and Subcutaneous Tissue Atropine effects such as dryness of skin and mucous membranes may occur.

Respiratory, thoracic and mediastinal disorders: Respiratory depression in children (atropine effect). Renal and Urinary Disorders Atropine effects such as urinary retention and difficulty in micturition may occur.

Eye disorder: Dilation of pupils with loss of accommodation, photophobia, increased intra-ocular pressure, very rarely angle closure glaucoma can occur.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at pv@searlecompany.com

OVERDOSE

Diagnosis

Overdosage can be life-threatening. Symptoms of overdosage may include opioid and/or anticholinergic effects including respiratory depression, coma, delirium, lethargy, dryness of the skin and mucous membranes, mydriasis or miosis, flushing, hyperthermia, tachycardia, hypotonia, tachypnea, toxic encephalopathy, seizures and incoherent speech.

Respiratory depression has been reported up to 30 hours after ingestion and may recur despite an initial response to narcotic antagonists.

Treat all possible Lomotil overdosages as serious and maintain medical observation/hospitalization until patients become asymptomatic without naloxone use.

Treatment

A pure narcotic antagonist (e.g., naloxone) should be used in the treatment of respiratory depression caused by Lomotil. Refer to the prescribing information for naloxone. Consider Lomotil toxicity even in settings of negative toxicology tests.

Following initial improvement of respiratory function, repeated doses of naloxone hydrochloride may be required to counteract recurrent respiratory depression

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties

The active ingredients diphenoxylate hydrochloride is a synthetic opioid derivative with selective effects on gastrointestinal smooth muscle. It is essentially devoid of "morphine type subjective effects" at therapeutic doses. Atropine sulphate is included in the formulation as an anti-abusing agent contributing to the safe use of the product. The dose of atropine sulphate contained in each tablet is subtherapeutic therefore a pharmaceutical effect due to atropine should not be detected taken at normal therapeutic doses.

Pharmacokinetic properties

Diphenoxylate hydrochloride is well absorbed from the gastrointestinal tract and extensively metabolized in the liver to diphenoxylate acid (difenoxin) and hydroxydiphenoxylic acid. It is excreted mainly as metabolites in the Urine and bile.

PRECLINICAL SAFETY DATA

Carcinogenesis, mutagenesis, impairment of fertility

No long-term study in animals has been performed to evaluate carcinogenic potential. Diphenoxylate hydrochloride was administered to male and female rats in their diets to provide dose levels of 4 and 20 mg/kg/day throughout a three-litter reproduction study. At 50 times the human dose (20 mg/kg/day), female weight gain was reduced and there was a marked effect on fertility as only 4 of 27 females became pregnant in three test breedings. The relevance of this finding to usage of Lomotil in humans is unknown

PRESENTATION

Lomotil tablet are available as a Boxes containing 500 tablets (25 x 20's blister strips)

INSTRUCTIONS

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

Protect from moisture, freezing, excessive heat & sunlight.

Keep out of the reach of children**.**

REGISTRATION NUMBER

Lomotil Tablets: 000012

MANUFACTURING LICENCE NO. 000016

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION – As per registrations letter

Manufactured by:

The Searle Company Limited

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

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