

PRESCRIBING INFORMATION

^N LOMOTIL* TABLETS

(2.5 mg diphenoxylate hydrochloride with 0.025 mg atropine sulfate, USP)

Anti-Diarrheal Agent

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Pfizer Canada Inc
17,300 Trans-Canada Highway
Kirkland, Quebec H9J 2M5

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(Diphenoxylate Hydrochloride with Atropine Sulfate, USP)

Anti-Diarrheal Agent

CLINICAL PHARMACOLOGY

The mode of action of diphenoxylate in the bowel is similar to that of morphine and related drugs. Gastrointestinal propulsion is inhibited through a direct action on the smooth muscle, resulting in a decrease in peristaltic action and a consequent increase in transit time.

INDICATIONS AND CLINICAL USE

LOMOTIL (diphenoxylate hydrochloride with atropine sulfate) is indicated as an adjunct in the management of diarrhea.

Bacterially-induced diarrhea should be treated with appropriate antimicrobial therapy.

CONTRAINDICATIONS

LOMOTIL (diphenoxylate hydrochloride with atropine sulfate) is contraindicated in patients with a known hypersensitivity to diphenoxylate hydrochloride or atropine sulfate, and in patients who are jaundiced.

LOMOTIL is contraindicated in the treatment of diarrhea associated with pseudomembranous enterocolitis. LOMOTIL is contraindicated for diarrhea caused by enterotoxin producing bacteria.

WARNINGS

THIS MEDICATION SHOULD BE KEPT OUT OF REACH OF CHILDREN SINCE ACCIDENTAL OVERDOSE MAY CAUSE SEVERE OR EVEN FATAL RESPIRATORY DEPRESSION. LOMOTIL (DIPHENOXYLATE HYDROCHLORIDE WITH ATROPINE SULFATE) IS NOT RECOMMENDED FOR USE IN CHILDREN UNDER TWO YEARS OF AGE. DOSAGE RECOMMENDATIONS SHOULD BE STRICTLY ADHERED TO, ESPECIALLY IN CHILDREN.

Use In Pregnancy

The use of LOMOTIL in women of childbearing potential or during pregnancy and lactation requires that the expected benefits of the drug be weighed against any possible hazard to the mother and child. Effects of diphenoxylate hydrochloride or atropine sulfate may be evident in the infants of nursing mothers taking LOMOTIL (since these compounds are excreted in breast milk).

PRECAUTIONS

General

LOMOTIL (diphenoxylate hydrochloride with atropine sulfate) may produce drowsiness or dizziness. The patient should be cautioned regarding activities that require mental alertness, such as driving or operating dangerous machinery. Slowing of intestinal motility by an agent such as LOMOTIL does not preclude the need for appropriate fluid and electrolyte replacement. Dehydration may further influence the variability of response to LOMOTIL and may predispose to delayed diphenoxylate intoxication. Drug-induced inhibition of peristalsis may result in fluid retention in the colon which may further aggravate dehydration and electrolyte imbalance. If severe dehydration or electrolyte imbalance is present, withhold LOMOTIL until appropriate corrective therapy has been initiated.

Use in Children

In children, LOMOTIL should be used with special caution, since signs of atropinism may occur even with recommended doses, particularly in patients with Down's Syndrome. LOMOTIL should be used with special caution in young children because of their variable response.

Patients with Special Diseases and Conditions

LOMOTIL should be used with extreme caution in patients with cirrhosis and other hepatic disease and in all patients with abnormal liver function tests, since hepatic coma may be precipitated.

In some patients with acute ulcerative colitis, agents which inhibit intestinal motility or delay 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 distension occurs or if other untoward symptoms develop.

Dependence Liability

Addiction to (dependency on) LOMOTIL is theoretically possible at high dosage. Therefore, the recommended dosage should not be exceeded. Because of the structural and pharmacological similarity of diphenoxylate to meperidine and similar drugs with a definite addiction potential, LOMOTIL should be administered with considerable caution to patients who are receiving addicting drugs, to individuals known to be addiction-prone, or to those whose histories suggest that they may increase the dosage on their own initiative. Because a subtherapeutic dose of atropine has been added to the diphenoxylate hydrochloride, to discourage deliberate overdose, there should be strict observance of the contraindications and precautions relative to the use of atropine.

Drug Interactions

LOMOTIL may potentiate the action of barbiturates, tranquilizers and alcohol. Therefore, the patient should be closely observed when these medications are used concomitantly.

Since the chemical structure of diphenoxylate is similar to that of meperidine, the concurrent use of LOMOTIL with monoamine oxidase inhibitors may in theory precipitate a hypertensive crisis.

ADVERSE EFFECTS

The most frequently reported adverse effect is nausea. Other symptoms which have been reported at therapeutic doses are:

Nervous System: Drowsiness, coma, lethargy, sedation/drowsiness, restlessness, dizziness, insomnia, headache, blurring of vision, depression, euphoria, confusion, paraesthesia, malaise.

Respiratory: Respiratory depression

GI: Vomiting, anorexia, nausea, abdominal bloating, cramps, paralytic ileus, toxic megacolon, pancreatitis.

Allergy: Anaphylaxis, pruritis, skin eruption, giant urticaria, angioneurotic edema.

Atropine effects such as dryness of the skin and mucous membranes, hyperthermia, tachycardia, urinary retention and flushing may also occur, especially in children.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

Symptoms

Initial signs of overdosage with LOMOTIL (diphenoxylate hydrochloride with atropine sulfate) may include dryness of the skin and mucous membranes, mydriasis, restlessness, flushing, hyperthermia and tachycardia followed by lethargy or coma, hypotonic reflexes, nystagmus, pinpoint pupils, and respiratory depression. Cardiac arrest has occurred in children.

Treatment

Treat all possible LOMOTIL overdoses as serious and maintain medical observation for at least 48 hours.

Gastric lavage, establishment of a patent airway, and possibly, mechanically-assisted respiration are advised. Gastric lavage should be undertaken with due caution in an unconscious patient, preferably following insertion of a cuffed endotracheal tube. If the patient is not comatose, administration of a slurry of activated charcoal may be indicated.

Narcotic antagonists such as Narcan (naloxone hydrochloride) may be used for the treatment of respiratory depression caused by narcotic drugs or pharmacologically-related compounds, such as LOMOTIL.

Narcan Dosage in Adults

Narcan (naloxone hydrochloride) may be administered to adults at a dose of 0.4 mg intravenously. Additional doses of 0.4 mg may be given at 2- or 3-minute intervals until adequate improvement in pulmonary ventilation is demonstrated. Subsequent injections of this drug must be governed by the degree of respiratory depression present and should be titrated accordingly. Since the duration of action of naloxone hydrochloride is short in comparison to that of diphenoxylate hydrochloride improvement of respiration after its administration may be followed by subsequent respiratory depression. It should be noted that although signs of overdose and respiratory depression may not be evident with LOMOTIL after ingestion, respiratory depression may occur 12 to 30 hours later. Consequently, continuous observation is necessary until the effect of diphenoxylate hydrochloride on respiration, which may persist for many hours, has passed. The period of observation should extend over at least 48 hours, preferably under continuous hospital care.

Narcan Dosage in Children

For known or suspected narcotic overdose, the initial dosage of Narcan in children is 0.005 - 0.01 mg/kg body weight when given intravenously, intramuscularly, or subcutaneously.

This dose can be repeated as for adults above. If necessary, Narcan can be diluted with Sterile Water for Injection.

DOSAGE AND ADMINISTRATION

Adults

The usual initial dose of LOMOTIL (diphenoxylate hydrochloride with atropine sulfate) is 5 mg (2 tablets) 3 or 4 times daily (20 mg/24 hrs in divided doses is the maximum recommended dosage). An individual maintenance dose can be subsequently determined. Downward adjustment should be made as soon as initial control of symptoms is accomplished. The maintenance dose may be as low as 1/4 of the dose required for initial control.

Children

NOT FOR USE IN CHILDREN UNDER TWO YEARS OF AGE (SEE WARNINGS AND PRECAUTIONS).

The recommended initial dosage of LOMOTIL determined by the child's weight, is as follows:

0.3 - 0.4 mg/kg daily in divided doses

For convenience, approximate dosage (in children of average weight) may be determined by the following table:

AGE	APPROXIMATE BODY WEIGHT	TOTAL DAILY DOSE
2 to 5 years	15 - 20 kg	2.5 mg 2 x a day
6 to 8 years	20 - 27 kg	2.5 mg 3 x a day
9 to 12 years	27 - 36 kg	2.5 mg 4 x a day
13 years & above	--	5 mg 4 x a day

As with adult therapy, adjustment of dosage downward should be made as soon as initial control of symptoms is accomplished.

These pediatric schedules are the best approximation of an average dose recommendation which should be adjusted according to the overall nutritional status and degree of dehydration encountered in the child. The recommended doses must not be exceeded.

AVAILABILITY OF DOSAGE FORMS

Tablets - Each white, round tablet with "SEARLE" debossed on one side and 61 on the other side, contains 2.5 mg of diphenoxylate hydrochloride and 0.025 mg of atropine sulfate.

Non-medicinal ingredients: acacia, corn starch, mineral oil, magnesium stearate, sorbitol, sucrose, talc.

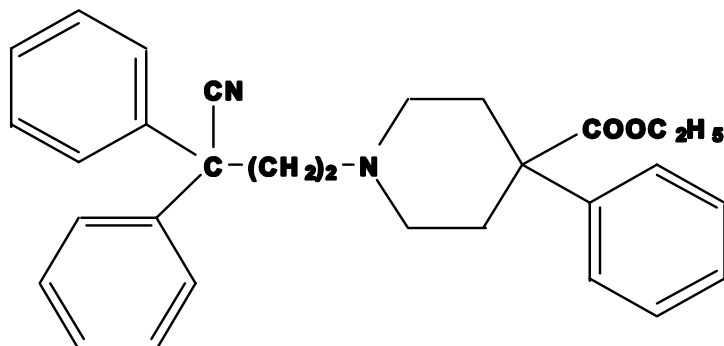
Tablets are available in bottles of 250.

Store at 15-25°C and protect from light.

LOMOTIL is a narcotic drug.

PHARMACEUTICAL INFORMATION

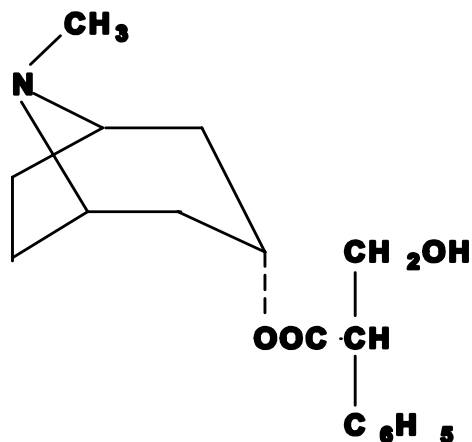
Proper Name: Diphenoxylate hydrochloride
Common Name: 1-(3-cyano-3,3-diphenylpropyl)-4-phenylpiperidine-4-carboxylate
Structural formula:



Empirical Formula: $C_{30}H_{32}N_2O_2 \cdot HCl$
Molecular Weight: 489.06
Physical Form: White, odorless crystalline powder
Solubility (at 25°C, mg/mL):
Acetic Acid 500
Chloroform 360
Methanol >50
Ethanol 3
Water 0.8

Melting Point: 220.5 - 222°C
pH: 3.3 (Saturated aqueous solution)
pKa: 7.1

Proper Name: Atropine sulfate
Common Name: tropan-3 α -ylrac-(2*R*)-3-hydroxy-2-phenylpropanoate
Structural formula:



Empirical Formula: 2 (C₁₇H₂₃NO₃)•H₂SO₄•H₂O
Molecular Weight: 694.84
Physical Form: Odorless, colourless crystals or white crystalline powder
Solubility: 1 g dissolves in 0.4 mL water
2.5 mL boil. alc.
2.5 mL glycerol
420 mL chloroform
3000 mL ether
Melting Point: 190 - 194°C
pH: 5.4
pKa: 9.9 (20°)