PRESCRIBING INFORMATION
Including Patient Medication Information

[N] LOMOTIL*

(diphenoxylate hydrochloride and atropine sulfate tablets USP, 2.5 mg / 0.025 mg)

Anti-Diarrheal Agent

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

Date of Preparation:
April 17, 2019

Control No. 222941

PRESCRIBING INFORMATION

[N] LOMOTIL*

(diphenoxylate hydrochloride and atropine sulfate tablets USP, 2.5 mg / 0.025 mg)

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 AND PRECAUTIONS

LOMOTIL (DIPHENOXYLATE HYDROCHLORIDE WITH ATROPINE SULFATE) IS NOT AN INNOCUOUS DRUG AND DOSAGE RECOMMENDATIONS SHOULD BE STRICTLY ADHERED TO, ESPECIALLY IN CHILDREN. LOMOTIL (DIPHENOXYLATE HYDROCHLORIDE WITH ATROPINE SULFATE) IS NOT RECOMMENDED FOR USE IN CHILDREN UNDER FOUR YEARS OF AGE. OVERDOSAGE MAY RESULT IN TACHYPNEA, SEIZURES, SEVERE RESPIRATORY DEPRESSION AND COMA, POSSIBLY LEADING TO PERMANENT BRAIN DAMAGE OR DEATH (SEE OVERDOSAGE). THEREFORE, KEEP THIS MEDICATION OUT OF THE REACH OF CHILDREN.

Use In Pregnancy and Lactation

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. Caution should be exercised when LOMOTIL is administered to a nursing mother, since diphenoxylate hydrochloride and atropine sulfate are excreted in breast milk. If a nursing mother is taking LOMOTIL, the infant may exhibit some effects of the drug.

General

LOMOTIL (diphenoxylate hydrochloride with atropine sulfate) may produce drowsiness or dizziness. The effect of LOMOTIL on the ability to drive or use machines has not been systematically evaluated. Patients should refrain from driving or using machines until they know that LOMOTIL does not negatively affect these abilities as confusional state, lethargy, sedation, somnolence, and dizziness may occur.

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.

Central Nervous System (CNS) depression, dizziness or drowsiness may be potentiated with the concomitant use of LOMOTIL with other CNS depressants such as 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.

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. LOMOTIL is not recommended for children under 4 years of age (see WARNINGS).

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 sulfate has been added to the diphenoxylate hydrochloride, to discourage deliberate overdosage, there should be strict observance of the contraindications and precautions relative to the use of atropine sulfate.

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.

CNS depression, dizziness or drowsiness may be potentiated with the concomitant use of LOMOTIL with other CNS-depressants.

ADVERSE EFFECTS

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

General Disorders:	Malaise
Nervous System:	Drowsiness, coma, lethargy, sedation/drowsiness, restlessness, dizziness, insomnia, headache, blurring of vision, depression, euphoria, confusion, paraesthesia, hallucination, somnolence
Respiratory:	Respiratory depression
GI:	Vomiting, anorexia, nausea, abdominal bloating, abdominal

	discomfort, cramps, paralytic ileus, toxic megacolon, pancreatitis, gastrointestinal disorder
Allergy:	Anaphylaxis, pruritis, skin eruption, giant urticaria, angioedema.

Atropine sulfate 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

If you think you have taken too much **LOMOTIL**, contact your healthcare professional, hospital emergency department or regional poison control centre immediately, even if there are no symptoms.

Diphenoxylate hydrocholoride with atropine sulfate should be kept in a child-resistant container and out of the reach of children since overdosage may lead to severe respiratory depression and coma, possibly leading to permanent brain damage or death (See WARNINGS).

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, tachypnea, toxic encephalopathy, seizures, and severe 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 Naloxone hydrochloride may be used for the treatment of respiratory depression caused by narcotic drugs or pharmacologically- related compounds, such as LOMOTIL.

Naloxone hydrochloride Dosage in Adults

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 overdosage 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.

Naloxone hydrochloride Dosage in Children

For known or suspected narcotic overdosage, the initial dosage of Naloxone hydrochloride 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, Naloxone hydrochloride 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 FOUR 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
4 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.

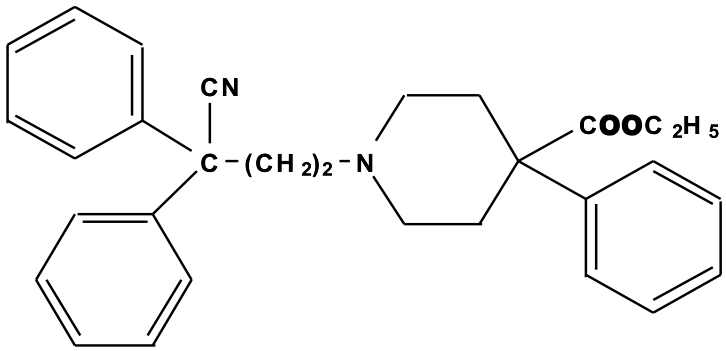
LOMOTIL is a narcotic drug.

PHARMACEUTICAL INFORMATION

Proper Name: Diphenoxylate hydrochloride

Common Name: 1-(3-cyano-3,3-diphenylpropyl)-4-phenylpiperidine-4-carboxylate

Structural formula:



Empirical Formula: $C_{30}H_{32}N_2O_2 \bullet HCl$

Molecular Weight: 489.06

Physical Form: White, odorless crystalline powder

Solubility (at 25ºC, mg/mL):

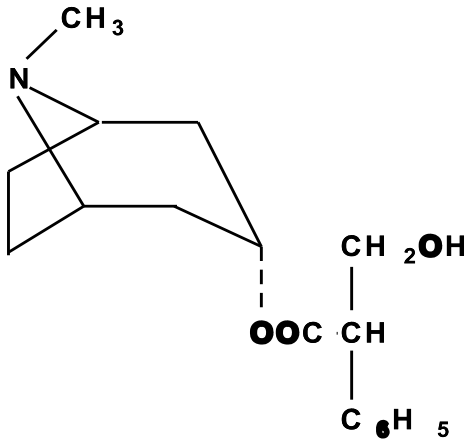
Acetic Acid	500
Chloroform	360
Methanol	>50
Ethanol	3
Water	0.8

Melting Point: 220.5 - 222°C

pH: 3.3 (Saturated aqueous solution)

pKa: 7.1

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



Empirical Formula:	2 $(C_{17}H_{23}NO_3)•H_2SO_4•H_2O$
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°)

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PATIENT MEDICATION INFORMATION

LOMOTIL
Diphenoxylate hydrochloride and atropine sulfate tablets USP

Read this carefully before you start taking **LOMOTIL** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **LOMOTIL**.

What is LOMOTIL used for?
- LOMOTIL is used along with other medicines to treat diarrhea.

How does LOMOTIL work?
- LOMOTIL reduces the movement of the muscles in your bowel. This slows down the movement of feces in your bowels.

What are the ingredients in LOMOTIL?
Medicinal ingredients: diphenoxylate hydrochloride and atropine sulfate.
Non-medicinal ingredients: acacia, corn starch, mineral oil, magnesium stearate, sorbitol, sucrose and talc.

LOMOTIL comes in the following dosage form:
As tablets containing 2.5 mg diphenoxylate hydrochloride and 0.025 mg atropine sulfate.

Do not use LOMOTIL if you:
- Are allergic to diphenoxylate hydrochloride or atropine sulfate.
- Are allergic to any of the other ingredients in LOMOTIL.
- Have jaundice which is a condition where your skin and the whites of your eyes are yellow.
- Have diarrhea caused by bacteria.

LOMOTIL is not recommended for children under the age of four.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take LOMOTIL. Talk about any health conditions or problems you may have, including if you:
- Have a history of dependence or addiction to alcohol, medicines or drugs.
- Are pregnant or planning to become pregnant.
- Are breastfeeding or planning to breastfeed.
- Are severely dehydrated or have an electrolyte imbalance.
- Have or have had liver problems.
- Have or have had a bowel disease called ulcerative colitis.

Other warnings you should know about:

Driving and using machines:

- LOMOTIL may cause drowsiness or dizziness. You should not drive or operate dangerous machinery when you first start to take this medicine.

Use in children:

- LOMOTIL is not recommended for children under the age of four. If your child's doctor has prescribed LOMOTIL they will monitor your child closely. Doctors must be very cautious when giving LOMOTIL to a child especially if the child has Down's syndrome. Talk to your doctor about the safe use of this product by your child.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with LOMOTIL:

- Medicines that may affect your nervous system such as:
    - Barbiturates like phenobarbital,
    - Benzodiazepines (medicines to help you sleep or reduce anxiety like lorazepam, alprazolam),
    - Sedatives (medicines to help you sleep),
    - Anxiolytics (medicines to help reduce anxiety),
    - Tranquilizers (medicines to help calm you down),
    - Muscle relaxants (medicines to help muscle spasms and back pain like methocarbamol, cyclobenzaprine),
    - General anesthetics (medicines used during surgery),
    - Antipsychotics (medicines used to treat schizophrenia or other psychiatric illness like olanzapine, clozapine, haloperidol),
    - Opioids (medicines used to treat pain like oxycodone, codeine, morphine, hydromorphone, meperidine, tramadol),
    - Alcohol,
    - Monoamine oxidase inhibitors, like phenelzine sulphate, tranylcypromine sulphate, moclobemide or selegiline, used to treat depression or Parkinson disease.

How to take LOMOTIL:

- Always take LOMOTIL exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.
- Swallow tablet whole with a glass of water.
- You should drink plenty of water while taking LOMOTIL.

Usual adult dose:

- The usual first dose is 2 tablets 3 or 4 times a day.
- Your doctor will decide how much LOMOTIL you should take after that and for how long you should take it.

Usual dose in children aged 4 and older:

- Your doctor will decide how much your child will receive. The dose they receive will be based on how much they weigh.

Overdose:

If you think you have taken too much **LOMOTIL**, contact your healthcare professional, hospital emergency department or regional poison control centre immediately, even if there are no symptoms.

What are possible side effects from using LOMOTIL?

These are not all the possible side effects you may feel when taking LOMOTIL. If you experience any side effects not listed here, contact your healthcare professional.

Side effects may include:

- Feeling ill
- Drowsiness
- Feeling tired
- Restlessness
- Dizziness
- Difficulty sleeping or sleepiness
- Headache
- Blurry vision
- Feeling unusually excited
- Confusion
- A feeling of pins and needles in your hands or feet or another body part
- Feeling depressed
- Loss of appetite, abdominal bloating, abdominal cramps, constipation.
- Dry skin
- Difficulty urinating

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
UNKNOWN FREQUENCY			
Respiratory depression (inadequate breathing): difficult or slow breathing.			√
Nervous System Effects: Depression, dizziness or drowsiness, sedation.		√	
Coma			√

Toxic megacolon (swelling of the colon): bloating of the abdomen, bloody or heavy diarrhea, fast heart rate, fever, painful bowel movements, shock, stomach pain, tenderness of the abdomen.			√
Pancreatitis (swelling of the pancreas): fast heart rate, fever, nausea, tenderness when touching the abdomen, upper abdominal pain, vomiting.		√	
Allergic reaction: difficulty breathing, difficulty swallowing, fever, hives, itchy skin, rash, swelling of your tongue, throat or face.			√
Hallucinations: seeing or hearing things that aren't there.		√	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (http://www.hc-sc.gc.ca/dhp-mps/medeff/report-declaration/index-eng.php) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:
Store between 15-25°C and protect from light.

Keep out of reach and sight of children.

If you want more information about LOMOTIL:

- Talk to your healthcare professional.
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (http://hc-sc.gc.ca/index-eng.php); the manufacturer's website (http://www.pfizer.ca), or by calling 1-

800-463-6001.

This leaflet was prepared by Pfizer Canada ULC.

Last Revised: April 17, 2019