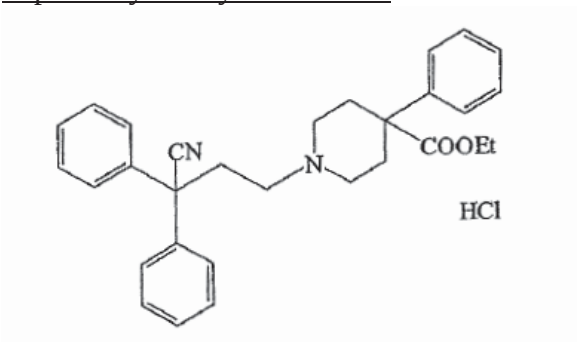
PRODUCT INFORMATION

LOMOTIL®

Diphenoxylate hydrochloride 2.5 mg and Atropine sulfate 25 microgram

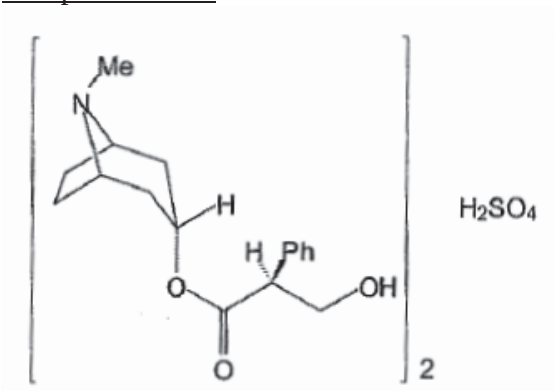
Name of the medicines

Diphenoxylate Hydrochloride:



$C_{30}H_{32}N_2O_2$, HCl M. W. = 489.1
CAS registry no.: 3810-80-8
Ethyl 1-(3-cyano-3,3-diphenylpropyl)-4-phenylpiperidine-4-carboxylate hydrochloride

Atropine sulfate:



$C_{34}H_{48}N_2O_{10}S$, H_2O M. W. = 695
CAS registry no.: 5908-99-6
Bis (1R, 3r, 5S)-3-[(RS)-(3-hydroxy-2-phenylpropionyl)oxy]-8-methyl-8-azabicyclo[3.2.1] octane sulphate

DESCRIPTION

Diphenoxylate hydrochloride is a white or almost white, crystalline powder, very slightly soluble in water, freely soluble in methylene chloride, sparingly soluble in alcohol, practically insoluble in ether.

Atropine sulfate is a white, crystalline powder or colourless crystals, very soluble in water, freely soluble from alcohol, practically insoluble in ether.

Each LOMOTIL® tablet contains diphenoxylate HCl (2.5mg) and atropine sulfate (25μg).

LOMOTIL contains the following excipients: acacia, magnesium stearate, liquid paraffin, sorbitol solution, sucrose and purified talc.

PHARMACOLOGY

Diphenoxylate is rapidly absorbed reaching peak blood levels in about two hours. Its relatively short plasma half-life (about 2.5 hours) and large plasma clearance suggest its rapid biotransformation. The major metabolic pathway of diphenoxylate in man is the hydrolysis of the ester group to give diphenoxylic acid – a pharmacologically active metabolite. Diphenoxylate metabolites probably undergo enterohepatic circulation. The drug is excreted principally as its metabolites in both urine and, to a larger extent, in the faeces.

Diphenoxylate is chemically related to the narcotic pethidine and acts by slowing intestinal motility. The formulation contains a small amount of atropine sulfate which has little therapeutic significance and is added to discourage excessive self-medication.

INDICATIONS

LOMOTIL® is indicated as an adjunctive therapy for acute and chronic diarrhoea.

CONTRAINDICATIONS

1. Known hypersensitivity to diphenoxylate HCl or atropine.
2. Jaundice
3. Diarrhoea associated with pseudomembranous enterocolitis which may occur during or up to several weeks following treatment with certain antibiotics.
4. Diarrhoea associated with inflammatory bowel disease, (eg ulcerative colitis, Crohn's disease) and bacterial and amoebic colitis, as diphenoxylate may exacerbate the underlying condition (see also under "WARNINGS").
5. LOMOTIL® is not recommended for children under 12 years of age. The medication should be kept out of reach of children since accidental overdosage may result in severe, even fatal respiratory depression.

WARNINGS

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. Diphenoxylate may have an additive effect on certain central nervous system depressants, e.g. barbiturates, tranquillizers and alcohol. Concurrent use with MAO inhibitors may, in theory, precipitate hypertensive crisis. Therefore close observation is required when these medications are given concomitantly with diphenoxylate hydrochloride. Bacterially-induced diarrhoea should be treated with appropriate antimicrobial therapy. In some patients with acute ulcerative colitis, agents which inhibit intestinal motility or prolong intestinal transit time have been reported to induce toxic megacolon.

APPROPRIATE FLUID AND ELECTROLYTE THERAPY SHOULD BE GIVEN TO PROTECT AGAINST DEHYDRATION. IF SEVERE DEHYDRATION OR ELECTROLYTE IMBALANCE IS PRESENT,

LOMOTIL® SHOULD BE WITHHELD UNTIL APPROPRIATE CORRECTIVE THERAPY HAS BEEN INITIATED, IN ORDER TO PREVENT DIPHENOXYLATE INTOXICATION DUE TO VARIABILITY OF RESPONSE.

KEEP OUT OF REACH OF CHILDREN. Initial signs of overdosage 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. Respiratory depression may be evidenced as late as 30 hours after ingestion and may recur in spite of an initial response to narcotic antagonists. **TREAT ALL POSSIBLE LOMOTIL® OVERDOSAGES AS SERIOUS AND MAINTAIN MEDICAL OBSERVATION FOR AT LEAST 48 HOURS.** Naloxone hydrochloride (Narcan^{R})[1] should be administered if respiratory depression develops. The action of naloxone hydrochloride is of shorter duration than that of diphenoxylate hydrochloride, so repeated injections of the antidote may be required. Establishment of a patent airway, and if necessary, artificial ventilation should be instituted. If the patient is not comatose gastric lavage and administration of a slurry of activated charcoal may be indicated.

PRECAUTIONS

The possibility of serious underlying aetiology should be considered before anti-diarrhoeal treatment of any type is instituted as other therapeutic measures may occasionally be necessary. Special caution should be exercised in treating diarrhoea which may be attributable to antibiotics known to cause colitis or pseudomembranous colitis.

Caution patients to adhere strictly to recommended dosage schedules.

Use in Pregnancy Pregnancy Category : **C**. Diphenoxylate is chemically related to the narcotic pethidine. Narcotic analgesics may cause respiratory depression in the newborn infant. This drug should not be given at, or near, term.

Use in Lactation Diphenoxylate hydrochloride may be and atropine sulphate is excreted in human breast milk; therefore infants of nursing mothers taking LOMOTIL® may exhibit some effects of the drug.

A subtherapeutic dose of atropine has been added to the diphenoxylate hydrochloride. Therefore, consideration should be given to the precautions relating to the use of atropine in children. LOMOTIL® should be used with caution since signs of atropinism may occur particularly in Down's Syndrome.

Addiction (dependency) to diphenoxylate hydrochloride is theoretically possible at high dosage. Therefore the recommended dosage should not be exceeded. Because of the structural and pharmacologic similarity of diphenoxylate hydrochloride to drugs with 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 they may increase the dosage on their own initiative.

[1] If naloxone HCl is not available, nalorphine HCl should be used.

ADVERSE EFFECTS

At therapeutic doses, the following have been reported:

Nervous system:	malaise/lethargy, confusion, sedation/drowsiness, dizziness, restlessness, depression, euphora, numbness of extremitiues, headache
Allergic:	Anaphylaxis, angioneurotic oedema, urticarial, swelling of gums, pruritis
Gastrointestinal system:	toxic megacolon, paralytic ileus, vomiting, nausea, anorexia, abdominal discomfort.

Atropine sulfate effects are: hyperthermia, tachycardia, urinary retention, flushing, dryness of the skin and mucous membranes.

DOSAGE AND ADMINISTRATION

The recommended adult starting dose is 5mg (two tablets) three or four times daily. After initial control is achieved, the dosage should be reduced to meet the requirements of the individual patient. Control may often be maintained with as little as 5mg (two tablets) daily.

OVERDOSAGE

In the event of overdosage (initial signs may include dryness of the skin and mucous membranes, restlessness, flushing, hyperthermia and tachycardia followed by lethargy or coma, hypotonic reflexes, nystagmus, pinpoint pupils and respiratory depression), gastric lavage, establishment of a patent airway and possibly mechanically assisted respiration are advised.

The narcotic antagonist, Narcan (naloxone hydrochloride) should be administered in the treatment of respiratory depression caused by narcotic analgesics or pharmacologically related compounds such as LOMOTIL®. When Narcan is administered intravenously the onset of action in generally apparent within two minutes. Narcan may also be administered subcutaneously or intramuscularly providing a slightly less rapid onset of action but a more prolonged effect.

To counteract the respiratory depression caused by LOMOTIL® overdosage, the following dosage schedule for Narcan should be followed:

> The usual initial adult dose of Narcan is 0.4mg (one mL) administered intravenously. If respiratory function does not adequately improve after the initial dose the same I.V. dose may be repeated at two to three minute intervals.

Following the initial improvement of respiratory function, repeat doses of Narcan may be required in response to recurrent respiratory depression.

Supplemental intramuscular doses of Narcan may be utilized to produce a longer lasting effect.

Since the duration of action of diphenoxylate hydrochloride is longer than that of naloxone hydrochloride improvement of respiration following administration may be followed by recurrent respiratory depression. 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.

It should be noted that, although signs of overdosage and respiratory depression may not be evident soon after ingestion of diphenoxylate hydrochloride, respiratory depression may occur from 12 to 30 hours later.

PRESENTATION AND STORAGE CONDITIONS

Tablets : White, uncoated, round, biconvex tablets marked "SEARLE" on one side and plain on the other, containing diphenoxylate hydrochloride 2.5mg, with atropine sulfate 25µg, in blister packs of 2's, 8's, 20's and 100's.

STORAGE: Store below 30°C.

NAME AND ADDRESS OF THE SPONSOR

iNova Pharmaceutical (Australia) Pty Ltd
Level 10, 12 Help Street
Chatswood, NSW 2067, Australia

POISON SCHEDULE OF THE MEDICINES

20 tablets	(S4) Prescription Only Medicine
100 tablets	(S4) Prescription Only Medicine
2 tablets	(S3) Pharmacist Only Medicine
8 tablets	(S3) Pharmacist Only Medicine

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (the ARTG)

13 February 1985

DATE OF MOST RECENT AMENDMENT

08 Oct 2014