

# AUSTRALIAN PRODUCT INFORMATION – LOFENOXAL® (DIPHENOXYLATE AND ATROPINE) TABLETS

## 1 NAME OF THE MEDICINE

Diphenoxylate hydrochloride and atropine sulfate

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each LOFENOXAL tablet contains diphenoxylate HCl 2.5 mg and atropine sulfate 25 micrograms.

Excipients with known effect:

- Sorbitol
- Sucrose

For the full list of excipients, see [Section 6.1 List of excipients](#).

LOFENOXAL is a white to off white, uncoated, round, biconvex tablet embossed “LT” on one side and plain on the other.

## 3 PHARMACEUTICAL FORM

Tablet

## 4 CLINICAL PARTICULARS

### 4.1 THERAPEUTIC INDICATIONS

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

### 4.2 DOSE AND METHOD OF ADMINISTRATION

The recommended adult starting dose is 5 mg (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 5 mg (two tablets) daily.

### 4.3 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, (e.g. ulcerative colitis, Crohn’s disease) and bacterial and amoebic colitis, as diphenoxylate may exacerbate the underlying condition (see [Section 4.4 Special Warnings and Precautions for Use](#)).

LOFENOXAL 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.

#### 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

##### **Interaction with CNS depressants**

Diphenoxylate may have an additive effect on certain central nervous system depressants, e.g. barbiturates, tranquillizers and alcohol (see [Section 4.5 Interactions with other medicines and other forms of interactions](#)).

##### **MAO Inhibitors**

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.

##### **Antibiotic use**

Bacterially induced diarrhoea should be treated with appropriate antimicrobial therapy.

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.

##### **Toxic megacolon in patients with acute ulcerative colitis**

In some patients with acute ulcerative colitis, agents which inhibit intestinal motility or prolong intestinal transit time have been reported to induce toxic megacolon.

##### **Dehydration and electrolyte imbalance**

**Appropriate fluid and electrolyte therapy should be given to protect against dehydration. If severe dehydration or electrolyte imbalance is present, LOFENOXAL should be withheld until appropriate corrective therapy has been initiated, in order to prevent diphenoxylate intoxication due to variability of response.**

Caution patients to adhere strictly to recommended dosage schedules.

##### **Dependence potential**

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, LOFENOXAL 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.

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.

##### **Atropinism**

LOFENOXAL should be used with caution since signs of atropinism may occur particularly in Down's Syndrome.

##### **Use in hepatic impairment**

LOFENOXAL 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.

### **Use in the elderly**

No data available.

### **Paediatric use**

LOFENOXAL 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 (see [Section 4.3 Contraindications](#)).

### **Effects on laboratory tests**

No data available.

## **4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS**

Diphenoxylate may have an additive effect on certain central nervous system depressants, e.g. barbiturates, tranquillizers and alcohol (see [Section 4.4 Special Warnings and Precautions for Use](#)).

## **4.6 FERTILITY, PREGNANCY AND LACTATION**

### **Effects on fertility**

No data available.

### **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 sulfate is excreted in human breast milk. Therefore, infants of nursing mothers taking LOFENOXAL may exhibit some effects of the drug.

## **4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES**

LOFENOXAL may cause dizziness or drowsiness. The effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration. However, patients should refrain from driving or using machinery until they know that LOFENOXAL does not negatively affect these abilities as confusion, lethargy, sedation, drowsiness and dizziness may occur (see [section 4.8. Adverse effects \(Undesirable effects\)](#)).

## **4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)**

At therapeutic doses, the following have been reported:

Nervous system:	malaise/lethargy, confusion, sedation/drowsiness, dizziness, restlessness, depression, euphoria, numbness of extremities, headache
Allergic:	Anaphylaxis, angioneurotic oedema, urticaria, 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.

### **Reporting suspected adverse effects**

Reporting suspected adverse reactions after registration 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 [www.tga.gov.au/reporting-problems](http://www.tga.gov.au/reporting-problems).

## **4.9 OVERDOSE**

### **Symptoms**

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.

### **Management**

**Treat all possible LOFENOXAL overdosages as serious and maintain medical observation for at least 48 hours.**

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.

Naloxone hydrochloride should be administered if respiratory depression develops. If naloxone hydrochloride is not available, nalorphine hydrochloride should be used.

When naloxone hydrochloride is administered intravenously the onset of action is generally apparent within two minutes. Naloxone hydrochloride 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 LOFENOXAL overdosage, the following dosage schedule for naloxone hydrochloride should be followed:

The usual initial adult dose of naloxone hydrochloride is 0.4 mg (1 mL) administered intravenously. The action of naloxone hydrochloride is of shorter duration than that of diphenoxylate hydrochloride, so repeated injections of the antidote may be required. 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.

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.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

## **5 PHARMACOLOGICAL PROPERTIES**

### **5.1 PHARMACODYNAMIC PROPERTIES**

#### **Mechanism of action**

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.

#### **Clinical trials**

No data available.

### **5.2 PHARMACOKINETIC PROPERTIES**

#### **Absorption**

Diphenoxylate is rapidly absorbed reaching peak blood levels in about two hours.

#### **Metabolism**

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.

#### **Excretion**

The drug is excreted principally as its metabolites in both urine and, to a larger extent, in the faeces.

### **5.3 PRECLINICAL SAFETY DATA**

#### **Genotoxicity**

No data available.

#### **Carcinogenicity**

No data available.

## **6 PHARMACEUTICAL PARTICULARS**

### **6.1 LIST OF EXCIPIENTS**

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

### **6.2 INCOMPATIBILITIES**

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

### 6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG).

### 6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 30°C.

### 6.5 NATURE AND CONTENTS OF CONTAINER

Blister pack: 20's

### 6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

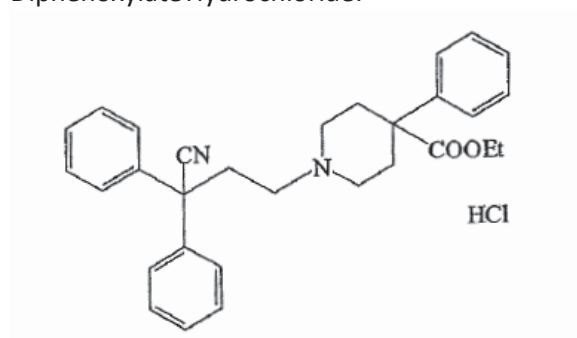
### 6.7 PHYSICOCHEMICAL PROPERTIES

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.

#### Chemical structure

Diphenoxylate Hydrochloride:

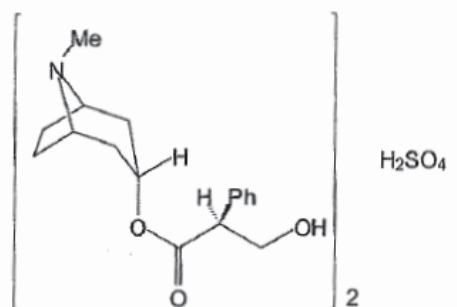


C<sub>30</sub>H<sub>32</sub>N<sub>2</sub>O<sub>2</sub>, HCl

M. W. = 489.1

Ethyl 1-(3-cyano-3,3-diphenylpropyl)-4-phenylpiperidine-4-carboxylate hydrochloride

Atropine sulfate:



$\text{C}_{34}\text{H}_{48}\text{N}_2\text{O}_{10}\text{S}$ ,  $\text{H}_2\text{O}$

M. W. = 695

Bis (1R, 3r, 5S)-3-[(RS)-(3-hydroxy-2-phenylpropionyl)oxy]-8-methyl-8-azabicyclo[3.2.1] octane sulphate

### CAS number

Diphenhydramine hydrochloride: 3810-80-8

Atropine sulfate: 5908-99-6

## 7 MEDICINE SCHEDULE (POISONS STANDARD)

(S4) Prescription Only Medicine

## 8 SPONSOR

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

Telephone: Toll-free 1800 630 056

## 9 DATE OF FIRST APPROVAL

13 February 1985

## 10 DATE OF REVISION

12 May 2020

### SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
All	Revised to the new Australian form for providing product information format and minor editorial changes.
2	Change to tablet appearance description