Version -5, 06/2017

DROPIZOL®

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Dropizol 10 mg/ml oral drops, solution

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml of oral liquid contains 1 ml of tincture from Papaver somniferum L., succus siccum (Opium, raw) corresponding to 10 mg of morphine.

1 drop contains 50 mg opium tincture corresponding to 0.5 mg (10 mg/ml) anhydrous morphine

1 ml = 19 drops

Extraction solvent: 33 % ethanol (V/V)

Excipients with known effect: 33 % ethanol (V/V)

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Oral drops, solution
Appearance: dark, reddish brown liquid.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Dropizol is indicated for severe diarrhoea such as diarrhoea caused by cytostatic medication, radiation or neuroendocrine tumours when use of other anti-diarrhoea treatments have not given sufficient effect.

4.2 Posology and method of administration

Posology
Adults: 5–10 drops, 2–3 times daily.
Individual doses should not exceed 1 ml, and the total daily dose should not exceed 6 ml

The posology should be individualized taking into account the patient's general condition, the patient's age, weight, and medical history (see sections 4.3 and 4.4).

Paediatric population
Dropizol should not be used in children and adolescents aged below 18 years for safety reasons.

Treatment should be initiated and supervised by a specialist.

Particular caution should be exercised when prescribing this drug due to its morphine content. The treatment period should be as short as possible.

Elderly

Caution should be exercised and the dosage initially reduced in treatment of elderly subjects.

Hepatic impairment
Morphine may precipitate coma in hepatic impairment – avoid or reduce dose. See Sections 4.3 and 4.4.

Renal impairment
Elimination is reduced and delayed in renal impairment - avoid or reduce dose.
See Sections 4.3 and 4.4.

Method of administration
Oral use.
The product can be used undiluted or mixed in a glass of water. After mixture with water, it should be used immediately. If the product is used undiluted the correct dosage can be administered with a spoon.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Opiate dependency.
- Glaucoma.
- Severe hepatic or renal impairment.
- Delirium tremens.
- Severe head trauma.
- Risk of paralytic ileus.

4.4 Special warnings and precautions for use

Dropizol should only be used following investigations of the etiology causing the symptoms and when first-line treatment has not given adequate results.

Dropizol drops should be used with caution in the following conditions / for the following patients

- The elderly
- Respiratory insufficiency (e.g. acute respiratory depression or Chronic Obstructive Airways Disease or asthma attack)
- Chronic renal disease and/or hepatic disease.
- Alcoholism.
- Biliary colic, cholelithiasis, biliary duct diseases
- Head injuries or increased intracranial pressure
- Reduced consciousness
- Heart failure secondary to lung disease
- Cardiorespiratory shock
- Monoamine oxidase inhibitors (including moclobemide), or within two weeks of their withdrawal
- Adrenocortical deficiency
- Hypothyroidism
- Low blood pressure with hypovolaemia
- Pancreatitis
- Prostatic hyperplasia and other conditions predisposing to urinary retention

A health care professional should be contacted in case of difficulty to urinate.

Adjustment of dose may be needed in the elderly, patients with thyroid insufficiency, and patients with mild to moderate renal or hepatic impairment (see also section 4.2 and 4.3).

Anti-diarrheals inhibiting peristalsis should be used with caution in patients with infection or inflammatory bowel diseases due to the increased risk of absorption of toxins, and of developing toxic megacolon and intestinal perforation. Due to the risk of paralytic ileus, Dropizol is not recommended before a surgical operation or within 24 hours after operation. If paralytic ileus is suspected during the use of Dropizol, the treatment must be stopped immediately.
Repeated administration may cause dependence and tolerance and the use of opium may lead to addiction to the substance. Particular caution should be exercised in individuals predisposed to addiction to narcotics and alcohol.

Administer at reduced doses and with the utmost caution to patients who are also being treated with other narcotic agents, sedatives, and tricyclic antidepressants and MAO-inhibitors (see also section 4.2).

Should only be used with caution in patients in high-risk groups, such as patients with epilepsy and hepatic disease.

4.5 Interaction with other medicinal products and other forms of interaction

Reduced consciousness and respiratory depression is potentiated by ethanol, hypnotics, general anaesthetics (e.g. barbiturates), MAO inhibitors and psychotropic drugs with a sedative action (e.g. fentiazines), gabapentin, antiemetic medications, antihistamines, and other opioids. Dropizol should not be used with other morphine agonists/antagonists (buprenorphine, nalbuphine, pentazocine) because of their competitive receptor-binding that may aggravate withdrawal symptoms and reduce therapeutic effect.

Due to the ethanol content, Dropizol should not be used concomitantly with disulfiram or metronidazole. Both of these drugs can cause disulfiram-like reactions (flushing, rapid breathing, tachycardia).

Midazolam increases the analgesic effect of morphine and buprenorphine, and increases the respiratory depression effect of morphine. It is expected that Midazolam will interact similarly with other opioids.

Rifampicin induces CYP 3A4 in the liver thus increasing the metabolism of morphine, codeine and methadone. The effect of these opioids is thereby decreased or counteracted.

Cimetidine decreases the metabolism of morphine.
Morphine inhibits the glucuronidation of zidovudine in vitro.

Morphine's duration of action may be reduced after taking fluoxetine.

Ethanol, see Section see 4.4.

4.6 Fertility, pregnancy and lactation

Pregnancy
Should be used with caution in pregnant women. Should not be used during the third trimester due to drowsiness and respiratory depression or withdrawal symptoms in the neonate.

Breastfeeding
Dropizol should not be used during breastfeeding, as opium passes into human milk. The milk to plasma concentration ratio is 1:4.

Fertility
As morphine has mutagenic propensity, it should be used for fertile women and men only if effective contraception is confirmed (see section 5.3).

4.7 Effects on the ability to drive and use machine
Due to its undesirable effects, Dropizol may have a major influence on the ability to drive and use machines.

4.8 Undesirable effect

Cardiac disorders Not known (cannot be estimated from the available data)	Tachycardia, bradycardia
Nervous system disorders Very common (≥1/10) Common (≥1/100 to <1/10) Not known (cannot be estimated from the available data)	Drowsiness Dizziness, Euphoria
Eye disorders Common (≥1/100 to <1/10)	Miosis
Respiratory, thoracic and mediastinal disorders Common (≥1/100 to <1/10) Uncommon (≥1/1,000 to <1/100)	Bronchospasms, cough decreased Respiratory depression
Gastrointestinal disorders Very common (≥1/10) Common (≥1/100 to <1/10)	Constipation, dry mouth Nausea, vomiting
Renal and urinary disorders Common (≥1/100 to <1/10) Uncommon (≥1/1,000 to <1/100)	Urinary retention Urethral spasm
Skin and subcutaneous tissue disorders Uncommon (≥1/1,000 to <1/100)	Pruritus
Musculoskeletal and connective tissue disorders Not known (cannot be estimated from the available data)	Involuntary muscle contractions
Vascular disorders Rare (≥1/10,000 to <1/1,000)	Orthostatic hypotension
General disorders and administration site conditions Common (≥1/100 to <1/10)	Astenia
Hepatobiliary disorder Uncommon (≥1/1,000 to <1/100)	Hepatic enzymes increased

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation 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 via HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2, Tel: +353 1 6764971, Fax: +353 1 6762517, Website: www.hpra.ie, e-mail: medsafety@hpra.ie

4.9 Overdose
Morphine toxicity. Lethal doses are primarily determined by the morphine content.

Symptoms:
Depressed level of consciousness increasing to coma. Respiratory depression (apnoea).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: ATC code: A 07 DA 02. Antipropulsives.

The constipating effect is caused by inhibition of the intestines' peristalsis.

Opium alkaloids (opioids and isoquinoline derivatives) induce constipation, euphoria, analgesia and sedation dependent on the dose and derivative.

5.2 Pharmacokinetic properties

Is absorbed from the gastrointestinal tract and is eliminated primarily as metabolites excreted in the urine. The duration of action is 3 to 4 hours.

5.3 Preclinical safety data

Studies have indicated an association between regular use of opium and increased risk of gastric adenocarcinoma and cancers in the oesophagus, larynx, bladder and lung. The mechanism of this association is not fully understood

Adverse reactions not observed in clinical studies, but seen in animals at exposures in excess of usual human exposure were as follows; Foetal growth retardation and increased rate of defects in the nervous system and the skeleton.
The relevance to clinical use is not known.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Ethanol 96% v/v
Purified water

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

30 months.

4 weeks after the bottle has been opened (in-use stability)

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions

6.5 Nature and contents of container

Brown glass bottle with a white LDPE dropper and white polypropylene (PP) childproof closure.

Pack sizes of 1 x 10 ml, 3 x 10 ml and 10 x 10 ml

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

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8. MARKETING AUTHORISATION NUMBER(S)

PA2245/001/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

<Date of first authorisation: {DD month YYYY}>

<Date of latest renewal: {DD month YYYY}>

10. DATE OF REVISION OF THE TEXT

<{MM/YYYY}>
<{DD/MM/YYYY}>
<{DD month YYYY}>