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 siccus (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 = 20 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

Symptomatic treatment of severe diarrhea in adults, when use of other anti-diarrhoea treatments have not given sufficient effect.

4.2 Posology and method of administration

Posology
Usual starting dose in 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 to use the lowest effective dose for the shortest duration of time 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, see section 5.1.

Treatment should be initiated and supervised by a specialist, e.g., oncologist or gastroenterologist.

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.
- Chronic obstructive pulmonary disease
- Acute asthma
- Severe respiratory depression with hypoxia and/or hypercapnia
- Heart failure secondary to lung disease (Cor pulmonale)
- Breastfeeding, see section 4.6

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
- Chronic renal disease and/or hepatic disease.
- Alcoholism.
- Biliary colic, cholelithiasis, biliary duct diseases
- Head injuries or increased intracranial pressure
- Reduced consciousness
- 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
- Concomitant administration of other antidiarrheal or antiperistaltic drugs, anticholinergics, antihypertensives, see section 4.5.
- Convulsive disorders
- Gastrointestinal haemorrhage

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).
Avoid use in older adults with a history of falls or fractures as ataxia, impaired psychomotor function, syncope, and additional falls may occur. If use is necessary, consider reducing use of other CNS-active agents that increase risk of falls and fractures and implement other strategies to reduce risk of falls.

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.

Risk from concomitant use of sedative medicines such as benzodiazepines or related drugs Concomitant use of Dropizol and sedative medicines such as benzodiazepines or related drugs may result in sedation, respiratory depression, coma and death. Because of these risks, concomitant prescribing with these sedative medicines should be reserved for patients for whom

alternative treatment options are not possible. If a decision is made to prescribe Dropizol concomitantly with sedative medicines, the lowest effective dose should be used, and the duration of treatment should be as short as possible.
The patients should be followed closely for signs and symptoms of respiratory depression and sedation. In this respect, it is strongly recommended to inform patients and their caregivers to be aware of these symptoms (see section 4.5).

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).
Oral P2Y12 inhibitor antiplatelet therapy
Within the first day of concomitant P2Y12 inhibitor and morphine treatment, reduced efficacy of P2Y12 inhibitor treatment has been observed (see section 4.5).

Sleep related breathing disorders.
Opioids can cause sleep-related breathing disorders including central sleep apnoea (CSA) and sleep-related hypoxemia. Opioid use increases the risk of CSA in a dose-dependent fashion.
In patients who present with CSA, consider decreasing the total opioid dosage.

Severe cutaneous adverse reactions (SCARs)
Acute generalized exanthematous pustulosis (AGEP), which can be life-threatening or fatal, has been reported in association with morphine treatment. Most of these reactions occurred within the first 10 days of treatment. Patients should be informed about the signs and symptoms of AGEP and advised to seek medical care if they experience such symptoms.
If signs and symptoms suggestive of these skin reactions appear, Dropizolshould be withdrawn and an alternative treatment considered.

Hepatobiliary disorders
Morphine may cause dysfunction and spasm of the sphincter of Oddi, thus raising intrabiliary pressure and increasing the risk of biliary tract symptoms and pancreatitis.

Opioid Use Disorder (abuse and dependence)
Tolerance and physical and/or psychological dependence may develop upon repeated administration of opioids such as Dropizol.
Repeated use of opioids can lead to Opioid Use Disorder (OUD). A higher dose and longer duration of opioid treatment, can increase the risk of developing OUD. Abuse or intentional misuse of opioidsl may result in overdose and/or death. The risk of developing OUD is increased in patients with a personal or a family history (parents or siblings) of substance use disorders (including alcohol use disorder), in current tobacco users or in patients with a personal history of other mental health disorders (eg. major depression, anxiety and personality disorders).
Before initiating treatment with Dropizol and during the treatment, treatment goals and a discontinuation plan should be agreed with the patient (see section 4.2). Before and during treatment the patient should also be informed about the risks and signs of OUD. If these signs occur, patients should be advised to contact their physician.
Patients will require monitoring for signs of drug-seeking behavior (e.g. too early requests for refills). This includes the review of concomitant opioids and psycho-active drugs (like
benzodiazepines). For patients with signs and symptoms of OUD, consultation with an addiction specialist should be considered.

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

Opioids may inhibit the hypothalamic–pituitary–adrenal (HPA) or gonadal axis at multiple levels and is most pronounced after long term use.
This may lead to symptoms of adrenal insufficiency (see also section 4.8).
This medicinal product contains 33 vol % ethanol (alcohol), i.e. up to 260 mg per dose, equivalent to 6.6 ml beer or 2.8 ml wine.

4.5 Interaction with other medicinal products and other forms of interaction

The risk of sedation, respiratory depression, coma or death increases because of additive CNS depressant effect by ethanol, hypnotics (e.g. zolpidem), general anaesthetics (e.g. barbiturates), MAO inhibitors (e.g. safinamide), tricyclic antidepressants and psychotropic drugs with a sedative action (e.g. phenothiazines), gabapentin or pregabalin, antiemetic medications (e.g. bromopride, meclizine, metoclopramide), antihistamines (e.g. carbinoxamine, doxylamine), and other opioids (e.g. alfentanil, butorphanol, fentanyl, hydrocodone, hydromorphone, levorphanol, meperidine, methadone, oxycodone, oxymorphone, remifentanil, sufentanil, tapentadol, tramadol). The dose and duration of concomitant use should be limited (see section 4.4).

Dropizol should not be used with other morphine agonists/antagonists (buprenorphine, nalbuphine, nalmefene, naltrexone, 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).

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.

A delayed and decreased exposure to oral P2Y12 inhibitor antiplatelet therapy has been observed in patients with acute coronary syndrome treated with morphine. This interaction may be related to reduced gastrointestinal motility and apply to other opioids. The clinical relevance is unknown, but data indicate the potential for reduced P2Y12 inhibitor efficacy in patients co- administered morphine and a P2Y12 inhibitor (see section 4.4). In patients with acute coronary syndrome, in whom morphine cannot be withheld and fast P2Y12 inhibition is deemed crucial, the use of a parenteral P2Y12 inhibitor may be considered.
Concurrent administration of morphine and antihypertensive drugs may increase the hypotensive effects of antihypertensive agents or other drugs with hypotensive effects.

Morphine inhibits the glucuronidation of zidovudine in vitro. Morphine's duration of action may be reduced after taking fluoxetine.
Cimetidine and ranitidine do not affect the bioavailability of opium, oral drops.

Otherdrug-druginteractions
Amphetamine and analogues can reduce the sedative effect of opioids. Loxapine and periciazine can increase the sedative effect of opioids. Concomitant use of flibanserin and opioids may increase the risk of CNS depression. Opioids can increase the plasma concentrations of desmopressin and sertraline.

Ethanol, see Section see 4.4.

4.6 Fertility, pregnancy and lactation

Pregnancy
There is limited amount of data from the use of opium in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3).
Dropizol is not recommended during pregnancy unless the benefits clearly outweigh the risks to both mother and child.
When morphine is used during pregnancy up to partition, neonatal withdrawal syndrome can occur.

Breastfeeding
Opium is excreted in human milk. If the patient is a ultra-rapid metaboliser of CYP2D6, higher levels of morphine (due to increased metabolism of codeine) may be present in breast milk and on very rare occasions may result in symptoms of opioid toxicity in the infant, which may be fatal. Dropizol is contraindicated during breastfeeding, (see section 4.3).

Fertility
There are insufficient data to assess human risk to fertility. Animal studies have shown chromosomal damage in reproductive cells (see section 5.3). Men and women of reproductive age should take necessary precautions.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

The adverse events reported for Dropizol drops are derived from literature and post-marketing experience with other morphine products.

Endocrine disorders Very rare /<1/10,000)	Syndrome of inadequate ADH-secretion (SIADH), Amenorrhoea
Not known (cannot be estimated from the available data)	Adrenal insufficiency
Psychiatric disorders	Addiction, dysphoric mood, restlessness,

Not known (cannot be estimated from the available data)	decreased libido or potency, hallucinations.
Nervous system disorders Very common (≥1/10) Common (≥1/100 to <1/10) Very rare (<1/10,000) Not known (cannot be estimated from the available data)	Drowsiness Dizziness, headache Muscle cramps, seizures, allodynia and hyperalgesia Euphoria
Eye disorders Common (≥1/100 to <1/10) Very rare (<1/10,000)	Miosis Blurred vision, diplopia, nystagmus
Cardiac disorders Uncommon (≥1/1,000 to <1/100)	Tachycardia, bradycardia, palpitations, facial flushing
Vascular disorders Rare (≥1/10,000 to <1/1,000)	Orthostatic hypotension
Respiratory,thoracic and mediastinal disorders Common (≥1/100 to <1/10) Uncommon (≥1/1,000 to <1/100) Very rare /<1/10,000) Not known (cannot be estimated from the available data)	Bronchospasms, cough decreased Respiratory depression Dyspnoea Central sleep apnoea syndrome
Gastrointestinal disorders Very common (≥1/10) Common (≥1/100 to <1/10) Rare (≥1/10,000 to <1/1,000) Very rare /<1/10,000) Not known (cannot be estimated from the available data)	Constipation, dry mouth Nausea, vomiting, loss of appetite, dyspepsia, dysgeusia Pancreatic enzymes increase and pancreatitis Ileus, abdominal pain Pancreatitis
Hepatobiliary disorder Uncommon (≥1/1,000 to <1/100) Rare (≥1/10,000 to <1/1,000) Not known (cannot be estimated from the available data)	Hepatic enzymes increased Biliary colic Spasm of sphincter of Oddi
Skin and subcutaneous tissue disorders Common (≥1/100 to <1/10) Uncommon (≥1/1,000 to <1/100) Very rare /<1/10,000) Not known (cannot be estimated from the available data)	Urticaria, sweating Pruritus Exanthema, peripheral oedema Acute generalised exanthematous pustulosis (AGEP)
Musculoskeletal and connective tissue disorders Not known (cannot be estimated from the available data)	Involuntary muscle contractions
Renal and urinary disorders Common (≥1/100 to <1/10) Uncommon (≥1/1,000 to <1/100) Rare (≥1/10,000 to <1/1,000)	Urinary retention Urethral spasm Renal colic
General disorders and administration site conditions Common (≥1/100 to <1/10) Rare (≥1/10,000 to <1/1,000) Very rare /<1/10,000) Not known (cannot be estimated from the available data)	Asthenia Withdrawal symptoms Feeling unwell, shivering Hyperthermia, vertigo

Description of selected adverse reactions

Drug Dependence

Repeated use of opioids can lead to drug dependence, even at therapeutic doses. The risk of drug dependence may vary depending on a patient's individual risk factors, dosage, and duration of opioid treatment (see section 4.4).

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
Website: www.hpra.ie

4.9 Overdose

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

Symptoms of overdose
Miosis, respiratory depression, somnolence, reduced skeletal muscle tone and drop in blood pressure. In severe cases circulatory collapse, stupor, coma, bradycardia and non-cardiogenic
lung oedema, hypotension and death may occur; abuse of high doses of strong opioids such as oxycodone can be fatal.

Therapy of overdose
Primary attention should be given to the establishment of a patent airway and institution of assisted or controlled ventilation. In the event of overdosing intravenous administration of an opiate antagonist may be indicated.
Furthermore, gastric lavage can be taken into consideration.

Supportive treatment (artificial respiration, oxygen supply, administration of vasopressors and infusion therapy) should, if necessary, be applied in the treatment of accompanying circulatory
shock.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: ATC code: A 07 DA 02. Antipropulsives.
Opium alkaloids (opioids and isoquinoline derivatives) induce constipation, euphoria, analgesia and sedation dependent on the dose and derivative.

These effects of are mediated by opioid receptors. The receptors are widely distributed in the central nervous system. Receptors are also present to a lesser extent, in vas deferens, knee
joints, the gastrointestinal tract, and in the heart and the immune system.

Opioid peptides modify the gastrointestinal (GI) function by interaction with opioid receptors on the enteric circuitries that control motility and secretion. Opioid receptors have been
localized in the GI tract of humans, but their relative distribution varies with GI layer and GI region1.

The micrograms-opioid receptor agonists inhibit gastric emptying, increases pyloric muscle tone, induce pyloric and duodenojejunal phasic pressure activity, disturb the migrating myoelectric complex, delay transit time through the small and large intestine and elevate the resting anal sphincter pressure. In addition to this, opioids attenuate the intestinal secretion of electrolytes and water and thereby facilitate the net absorption of fluid. In addition to this, the microgram, κ and δ-opioid receptors contribute to opioid-inhibition of muscle activity in the intestine. The result of all these effects is constipation.

The use of opium is well-established for treatment of diarrhoea in the clinic. Controlled clinical studies is not available.

No clinical trials in the paediatric population have been performed and the product is not considered suitable in this population because of safety concerns, see section 4.2.

5.2 Pharmacokinetic properties

Absorption
Peak serum concentrations of morphine, the main alkaloid of the opium extract, are achieved within 2 to 4 hours after oral administration.

Distribution
After absorption, morphine is bound to plasma proteins in the proportion of 30 %.

Biotransformation
Opium alkaloids are extensively metabolized to glucuronide conjugates (3-glucuronide (M3G) and 6-glucuronide (M6G)) that undergo an enterohepatic cycle. 6-glucuronide is a metabolite of morphine about 50 times more active than the parent substance. Morphine is also demethylated, which leads to another active metabolite, normorphine.

Codeine is metabolized to give codeine-6-glucuronide, morphine (the only active metabolite) and norcodeine. Since codeine is present in opium extract at levels ten times lower than those of morphine, its hepatic transformation has little effect on the overall bioavailability of morphine.

Elimination
The elimination half-life of morphine is approximately 2 hours. An elimination half-life of 2.4 to 6.7 hours has been reported for M3G. About 90 % of total morphine is excreted in 24 hours
with traces in urine for 48 hours or more 9.

The elimination of glucuronoconjugate derivatives is essentially by the urinary route, both by glomerular filtration and tubular secretion. Faecal elimination is low (<10 %).

5.3 Preclinical safety data

Several studies have shown that morphine induces chromosome damage in animals in somatic and germ cells and in human somatic cells. A genotoxic potential for humans is therefore
expected. Long-term animal studies on the carcinogenic potential of morphine have not been conducted.

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.

Animal studies have shown reproductive toxicity during the whole pregnancy (CNS malformations, foetal growth retardation, skeleton defects, testis atrophy, changes in neurotransmitter systems and behaviour, dependency.

In addition, morphine had an effect on the fertility of male offspring. Animal studies have further shown that morphine can bring damage to sex organs or gametes and by endocrine
disruption can adversely affect male and female fertility.

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

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

6.4 Special precautions for storage

Do not refrigerate or freeze.

6.5 Nature and contents of container

Brown glass bottle with a white LDPE dropper and white polypropylene (PP) child-resistant closure.

Pack sizes of 1 x 10 ml, 2 x 10 ml, 3 x 10 ml, 4 x 10 ml, 5 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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Ørestads Boulevard 108, 5
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Denmark

8 MARKETING AUTHORISATION NUMBER

PA2245/001/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 22nd June 2018
Date of last renewal: 15th July 2022

10 DATE OF REVISION OF THE TEXT

October 2024