1.3.1.1.1 Professional Information

SCHEDULING STATUS

S6

1 NAME OF THE MEDICINE

Dropizol 10 mg/ml oral drops, solution.

2 QUALITIVE AND QUANTITIVE 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 diarrhoea in adults, when use of other anti-diarrhoea treatments have not given sufficient effect.

4.2 Posology and method of administration

Posology

25 *21/01/2025*
Initial/ Date

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 individualised 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).

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

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

Special populations

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).

Paediatric population

Dropizol should not be used in children and adolescents aged below 18 years for safety reasons (see section 5.1).

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.

25 *21/01/2025*

Initial/ Date

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients.
- 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.

25 *21/01/2025*
Initial/ Date

- 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 antidiarrhoeal 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 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-diarrhoeals 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.



25 21/01/2025

Initial/ Date

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 medicines

Concomitant use of Dropizol and sedative medicines such as benzodiazepines or related medicines 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).

Dropizol should be administered 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 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).

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

25 *21/01/2025*
Initial/ Date

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 Section 4.8).

This medicine 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 medicines 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 medicines with a sedative action (e.g. phenothiazines), gabapentin, 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 medicines 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.

25 *21/01/2025*
Initial/ Date

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 medicines may increase the hypotensive effects of antihypertensive agents or other medicines 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.

Other drug-drug interactions

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 4.4.

4.6 Fertility, pregnancy and lactation

Pregnancy

There is limited amount of data from the use of opioids in pregnant women. Studies in animals have shown reproductive toxicity, therefore genotoxic potential in humans is expected (see Section 5.3).

25 *21/01/2025*
Initial/ Date

Dropizol should be used with caution during pregnancy, and practitioners must be aware of the risk of neonatal withdrawal syndrome as an adverse effect.

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 may result in symptoms of opioid toxicity in the neonate, 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

a. Summary of the safety profile

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

Tabulated list of adverse reactions

Endocrine disorders	

25 *21/01/2025*
Initial/ Date

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 Not known (cannot be estimated from the available data)	Addiction, dysphoric mood, restlessness, 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)	 Bronchospasms, cough decreased Respiratory depression Dyspnoea
Gastrointestinal disorders	

25 *21/01/2025*
Initial/ Date

Very common (≥ 1/10)	Constipation, dry mouth
Common (≥ 1/100 to < 1/10)	Nausea, vomiting, loss of appetite, dyspepsia, dysgeusia
Rare (≥ 1/10 000 to <1/1 000)	Pancreatic enzymes increase and pancreatitis
Very rare /< 1/10 000)	Ileus, abdominal pain
Hepatobiliary disorder	
Uncommon (≥ 1/1 000 to < 1/100)	Hepatic enzymes increased
Rare (≥ 1/10 000 to < 1/1 000)	Biliary colic
Skin and subcutaneous tissue disorders	
Common (≥ 1/100 to < 1/10)	Urticaria, sweating
Uncommon (≥ 1/1 000 to < 1/100)	Pruritus
Very rare /< 1/10 000)	Exanthema, peripheral oedema
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)	Urinary retention
Uncommon (≥ 1/1 000 to < 1/100)	Urethral spasm
Rare (≥ 1/10 000 to < 1/1 000)	Renal colic
General disorders and administration site conditions	
Common (≥ 1/100 to < 1/10)	Asthenia
Rare (≥ 1/1 000 to < 1/1 000)	Withdrawal symptoms
Very rare /< 1/10 000)	Feeling unwell, shivering

25 *21/01/2025*
Initial/ Date

Not known (cannot be estimated from the available data)	Hyperthermia, vertigo

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine.

Health care providers are requested to report any suspected adverse drug reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

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. 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

25 *21/01/2025*
Initial/ Date

Category and class: 11.10 Medicines acting on gastro-intestinal tract- Other

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

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 region 1.

The μ-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 μ, 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



25 *21/01/2025*

Initial/ Date

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 metabolised 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 metabolised 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

25 *21/01/2025*
Initial/ Date

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.

25 *21/01/2025*

Initial/ Date

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

6.4 Special precautions for storage

Store at or below 25 °C.

This medicine does not require any special storage conditions.

Store in the original container.

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 of a used medicine or waste materials derived from such medicine and other handling of the product

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

7 THE HOLDER OF THE CERTIFICATE OF REGISTRATION

Key Oncologics (Pty) Ltd

39 Eleventh Avenue

Houghton Estate, 2198

Johannesburg

8 REGISTRATION NUMBER(S)

56/11.10/1062

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

25 *21/01/2025*

Initial/ Date

21 January 2025

10 DATE OF REVISION OF TEXT

21 January 2025

25 *21/01/2025*
Initial/ Date