1.3.1.1 Proposed Professional Information

SCHEDULING STATUS S 6

1 NAME OF THE MEDICINE

Oramorph® Oral Drops 20 mg/ml, 20mg/ml, Solution

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Morphine sulphate.

1 ml oral drops, solution contains 20 mg morphine sulphate, corresponding to 15 mg morphine.

Sugar free.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Oral solution.

A clear colourless liquid.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

For the relief of severe pain in adults.

4.2 Posology and method of administration

Posology

The dosage of Oramorph® Oral Drops 20mg/ml must be adapted to the severity of pain and to the individual sensitivity of the patient.

The recommended range of the single and daily doses is stated in the following table based on a single dose of 0,2 to 0,3 mg morphine sulphate/kg body weight.

Age	**Single dose**	**Total daily dose**
Adults	0,5-3 ml, i.e. 8-48 drops of Oramorph® Oral Drops	Up to 18 ml, i.e. 288 drops of Oramorph® Oral Drops

	20mg/ml, corresponding to 10-60 mg morphine sulphate	20mg/ml, corresponding up to 360 mg morphine sulphate

The dose is removed from the 20 ml bottle by counting the drops (1 drop = 1,25 mg morphine sulphate).

In case of decreasing effect, the single doses can be repeated after 4-6 hours.

The maximum daily doses should not exceed the single doses by more than 4 to 6-fold.

If higher daily doses are required, other suitable active ingredient strengths may be used alternatively or in combination with Oramorph® Oral Drops 20 mg/ml.

Special populations

Renal or hepatic impairment

In patients with impaired liver or kidney function and in those with suspected delayed gastrointestinal passage Oramorph® Oral Drops 20mg/ml should be dosed with special caution.

Elderly patients

Elderly patients (usually 75 years and older) and patients with poor overall physical condition may be more sensitive to morphine. Therefore, the adjustment of dose must be done more carefully and/or the dosage intervals must be extended. As appropriate, lower dosage strengths must be given instead.

Special recommendations concerning dose adjustment

For initial dose adjustment, pharmaceutical forms with lower active ingredient content may be applied, possibly also in addition to an existing therapy with prolonged-release tablets.

In principle, the administered dose should be sufficiently high and at the same time the lowest dose needed for pain relief in the individual case should be aimed at.

For treatment of chronic pain dosing following a fixed time schedule is preferred.

In patients receiving another additional analgesic treatment (e. g. surgery, plexus blockage) the dose should be readjusted following the respective measure.

Method of administration

For oral use.

The oral drops solution is administered with a sufficient quantity of liquid. The medication can be taken independently of meals.

The medical practitioner decides about the duration of the treatment dependent on the pain. Oramorph® Oral Drops 20mg/ml should not be given longer than absolutely necessary.

If prolonged analgesic treatment with Oramorph® Oral Drops 20mg/ml appears necessary based on the nature and severity of the disease, careful and regular monitoring within short time intervals should be installed (if required by means of temporary suspension of the medication) to evaluate if and to what extent the therapeutic necessity persists. If needed, more suitable pharmaceutical forms should be applied instead. In case of chronic pain conditions, a fixed dosage regimen is preferred.

Discontinuation of therapy

Since the risk of occurrence of withdrawal symptoms is increased in case of abrupt discontinuation of therapy the dose should be reduced stepwise after termination of treatment.

4.3 Contraindications

Oramorph® Oral Drops 20mg/ml is contraindicated in:

- patients known to be hypersensitive to morphine or to any of the excipients listed in section 6.1
- ileus
- acute abdomen
- head injury or raised intracranial pressure with a decrease in the level of consciousness, unless ventilation is performed
- patients with compromised airways
- pregnancy and lactation

4.4 Special warnings and precautions for use

Careful monitoring by the medical practitioner and possibly dose reduction is needed in case of:

- opioid dependence
- impaired consciousness from any cause
- conditions associated with a disturbance of the respiratory centre and of the respiratory function or where such disturbances must be avoided
- cor pulmonale
- conditions with increased intracranial pressure unless ventilation is performed
- hypotension in the setting of hypovolaemia
- prostatic hyperplasia with residual urine (risk of bladder rupture due to urinary retention)
- obstruction or spasms of urinary tracts
- diseases of biliary ducts
- obstructive and inflammatory bowel diseases
- phaeochromocytoma
- pancreatitis
- hypothyroidism
- epilepsy or increased propensity to seizures.

In case of an opioid overdose, respiratory depression is the most important risk (see section 4.9).

Dependence and withdrawal (abstinence) syndrome

Use of opioid analgesics may be associated with the development of physical and/or psychological dependence or tolerance. The risk increases with the time the medicine is used, and with higher doses. Drug withdrawal syndrome may occur upon abrupt cessation of therapy or dose reduction. Symptoms can be minimised with adjustments of dose or dosage form, and gradual withdrawal of morphine. For individual symptoms (see section 4.8).

Therapeutic administration in patients with chronic pain is associated with a markedly reduced risk of psychological dependence and must be assessed carefully.

Morphine has an abuse potential similar to other strong agonist opioids, and should be used with

particular caution in patients with a history of alcohol or drug abuse.

Post-operative treatment

Compared to patients not undergoing surgery, the use of Oramorph® Oral Drops 20mg/ml solution is associated with an increased risk of ileus or respiratory depression during the postoperative phase and should therefore be administered with caution in patients before and after surgery.

Due to the analgesic effect of morphine serious intra-abdominal complications such as bowel perforation can be masked.

Adrenal insufficiency

Opioid analgesics may cause reversible adrenal insufficiency requiring monitoring and glucocorticoid replacement therapy. Symptoms of adrenal insufficiency may include e.g. nausea, vomiting, loss of appetite, fatigue, weakness, dizziness, or low blood pressure.

In case of pre-existing adrenocortical insufficiency (e.g. Morbus Addison), plasma concentrations of cortisol should be monitored and possibly corticoids should be substituted.

Acute chest syndrome (ACS) in patients with sickle cell disease (SCD)

Due to a possible association between ACS and morphine use in SCD patients treated with morphine during a vaso-occlusive crisis, close monitoring for ACS symptoms is warranted.

Decreased Sex Hormones and increased prolactin

Long-term use of opioid analgesics may be associated with decreased sex hormone levels and increased prolactin. Symptoms include decreased libido, impotence or amenorrhea.

Women of childbearing potential / Contraception in males and females

Due to its mutagenic properties, morphine should be given to males with procreative potential and to females with childbearing potential only if effective contraceptive measures are guaranteed (see section 4.6).

Hyperalgesia

Hyperalgesia that does not respond to a further dose increase of morphine may occur in particular in high doses. A morphine dose reduction or change in opioid may be required.

Risk from concomitant use of sedative medicines such as benzodiazepines or related medicines

Concomitant use of Oramorph® Oral Drops 20mg/ml 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 Oramorph® Oral Drops 20mg/ml 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).

Use with rifampicin

Plasma concentrations of morphine may be reduced by rifampicin. The analgesic effect of morphine should be monitored and doses of morphine adjusted during and after treatment with rifampicin.

Drug testing

The use of Oramorph® Oral Drops 20mg/ml can lead to positive results of doping control or drug testing.

Paediatric population

Oramorph® Oral Drops 20mg/ml is not recommended for use in children.

4.5 Interaction with other medicinal products and other forms of interaction

The following interactions of this medicinal product must be considered:

Concomitant application of morphine and other medicines with centrally sedating effects such as tranquilisers, anaesthetics, hypnotics and sedatives, neuroleptics, barbiturates, antidepressants, antihistamines or antiemetics, and other opioids or alcohol can result in an increase of the adverse effects of morphine at the usually recommended dose. This applies especially to the possibility of respiratory depression, sedation, hypotension and even coma.

Sedative medicines such as benzodiazepines or related medicines

The concomitant use of opioids with sedative medicines such as benzodiazepines or related medicines increases the risk of sedation, respiratory depression, coma and death because of additive CNS depressant effect. The dose and duration of concomitant use should be limited (see section 4.4).

Anticholinergics

Medicines with anticholinergic effect (e.g. psychotropic medicines, antihistamines, antiemetics, medicines for the treatment of Morbus Parkinson) can enhance anticholinergic adverse effects of opioids (e.g. constipation, dry mouth or disturbances of micturition).

Cimetidine

Cimetidine and other medicines impairing liver metabolism can lead to higher morphine plasma concentrations due to the inhibition of its metabolism.

Muscle relaxants

Morphine can enhance the effect of muscle relaxants.

Monoamine oxidase inhibitors

In patients pre-treated with certain antidepressants (MAO inhibitors) within 14 days prior to initiation of opioids life-threatening interactions affecting the central nervous system, the respiratory and the circulatory function have been observed in relation to pethidine. Comparable effects related to morphine cannot be excluded.

Rifampicin

Concomitant application of rifampicin can lead to a decrease in the effect of morphine.

Paediatric population

The similarity of interactions to adults has not been establised.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential / Contraception in males and females

Due to its mutagenic properties, morphine should be given to males with procreative potential and to females with childbearing potential only if effective contraceptive measures are guaranteed (see section 4.4).

Pregnancy

The use of Oramorph® Oral Drops 20mg/ml is contraindicated during pregnancy (see section 4.3).

Infants born to mothers taking Oramorph® Oral Drops 20mg/ml may suffer withdrawal reactions.

Breastfeeding

The use of Oramorph® Oral Drops 20mg/ml is contraindicated during lactation (see section 4.3).

Since clinically relevant concentrations can be reached in infants, mothers taking Oramorph® Oral Drops 20 mg/ml should not breastfeed their infants.

Fertility

Animal studies have shown that morphine may reduce fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

Morphine can impair the attentiveness and the capability to react to such an extent that the ability to drive or to use machines is impaired. This is to be expected especially upon initiation of treatment, dose increase and change in medication as well as in combination with alcohol or the use of sedatives.

The assessment of the individual situation in each case must be done by the treating medical practitioner. During a stable therapeutic regimen driving is not prohibited generally.

4.8 Undesirable effects

a) Summary of the safety profile

Data from clinical trials are not available. Therefore, except where stated all frequencies of the undesirable effects are unknown.

In normal doses, the commonest side effects of morphine sulphate are nausea, vomiting, constipation, drowsiness and confusion. If constipation occurs, this may be treated with appropriate laxatives. The effects of morphine have led to its abuse and misuse. Dependence and addiction may develop with regular, use.

b) Tabulated summary of adverse reactions

SYSTEM ORGAN CLASS	**FREQUENCY**	**ADVERSE REACTIONS**
Immune system disorders	Frequency unknown	Anaphylactic and anaphylactoid responses
Endocrine disorders	Less frequent	Syndrome of inappropriate antidiuretic hormone secretion (SIADH[a])
Metabolism and nutrition disorders	Frequent	Anorexia
Psychiatric disorders[b]	Frequent	Emotional and mood disturbances not elsewhere classified (NEC[c])
	Frequent	Agitation[d] Insomnia Cognitive and attention disorders and

SYSTEM ORGAN CLASS	**FREQUENCY**	**ADVERSE REACTIONS**
		disturbances[e] Sensory disturbances
	Less frequent	Drug dependence[f] Libido decreased Potency disturbance
Nervous system disorders[g]	Frequent	Sedation Headache Dizziness Taste alteration
	Less frequent	Tremor Muscle contractions involuntary Epileptic seizure
	Frequency unknown	Allodynia[h] Hyperalgesia[f,h]
Eye disorders	Less frequent	Blurred vision Diplopia Nystagmus Miosis
Cardiac disorders	Less frequent	Blood pressure increased Heart rate increased Palpitations Cardiac failure
	Less frequent	Dyspnoea
Vascular disorders	Frequency unknown	Non-cardiogenic pulmonary oedema[i]

SYSTEM ORGAN CLASS	**FREQUENCY**	**ADVERSE REACTIONS**
Respiratory, thoracic and mediastinal disorders	Less frequent	Bronchospasm
Gastrointestinal disorders	Frequent	Nausea[j] Dry mouth[j] Obstipation[k]
	Frequent	Vomiting[l] Dyspepsia
	Less frequent	Pancreatitis
	Less frequent	Ileus Abdominal pain
Hepato-biliary disorders	Less frequent	Colic biliary
	Less frequent	Hepatic enzymes increased
Skin and subcutaneous tissue disorders	Frequent	Urticaria[m] Pruritis[m]
	Less frequent	Exanthema[n] Peripheral oedema[n]
Musculoskeletal and connective tissue disorders	Less frequent	Muscle cramps Muscle rigidity Chills
Renal and urinary disorders	Frequent	Micturition disorder
	Less frequent	Renal colic
Reproductive system and breast disorders	Less frequent	Amenorrhoea
General disorders and administration site	Less frequent	Facial flushing Weakness generalised[o]

SYSTEM ORGAN CLASS	**FREQUENCY**	**ADVERSE REACTIONS**
conditions		Drug tolerance
	Less frequent	Drug withdrawal syndrome
	Less frequent	Asthenia Malaise
	Frequency unknown	Hyperhidrosis
Investigations	Less frequent	Pancreatic enzymes increased

a. Syndrome of inadequate ADH secretion, with hyponatraemia as the main symptom.
b. Morphine shows various psychiatric undesirable effects which with regard to severity and nature present differently (depending on the personality and duration of therapy).
c. Mood changes, mostly euphoria, but also dysphoria.
d. Changes in activity, mostly sedation but also enhanced activity or agitation.
e. Such as, disturbances in thinking, altered apprehensiveness/hallucinations, confusion.
f. See section 4.4.
g. Depending on the dose, morphine leads to various extents of respiratory depression and sedation ranging from slight fatigue to giddiness.
h. Especially in high doses hyperalgesia or allodynia (see section 4.4), which do not respond to a further increase in morphine doses (possibly dose reduction or opioid rotation is necessary).
i. Reported in patients treated under intensive-care conditions.
j. Dose dependant.
k. Typical accompanying symptom of long-term treatment.
l. Especially at the beginning of therapy.
m. Hypersensitivity reaction.
n. Reversible upon termination of therapy.
o. Weakness generalised to loss of consciousness.

c) Description of selected adverse reactions

Drug dependence and withdrawal (abstinence) syndrome

Use of opioid analgesics may be associated with the development of physical and/or psychological dependence or tolerance. An abstinence syndrome may be precipitated when opioid administration is suddenly discontinued or opioid antagonists administered, or can sometimes be experienced between doses. For management, see 4.4.

Physiological withdrawal symptoms include: Body aches, tremors, restless legs syndrome, diarrhoea, abdominal colic, nausea, flu-like symptoms, tachycardia and mydriasis. Psychological symptoms include dysphoric mood, anxiety and irritability. In drug dependence, “drug craving” is often involved.

d) Paediatric population

Frequency, type and severity of adverse reactions in children are expected to be the same as in adults.

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 asked to report any suspected adverse reactions to SAHPRA via the “**6.04 Adverse Drug Reactions Reporting Form**”, found online under SAHPRA’s publications: https://www.sahpra.org.za/Publications/Index/8.

4.9 Overdose

Symptoms of intoxication

The sensitivity towards morphine varies greatly from patient to patient. Therefore, symptoms of intoxication can occur in adults after application of single doses which correspond to a subcutaneous and intravenous dose of about 30 mg. In patients with carcinoma these doses are frequently exceeded without provoking serious adverse reactions.

The manifestation of an opioid intoxication comprises the triad of miosis, respiratory depression and coma. At first pinpoint pupils are observed; however, in case of marked hypoxia the pupils are dilated.

Respiration is markedly reduced (breath rate of 2-4 per minute). The patient becomes cyanotic.

Morphine overdosage leads to giddiness and stupor up to coma. The blood pressure remains normal initially but decreases markedly with progression of intoxication. Persistent decrease in blood pressure can result in shock. Tachycardia, bradycardia and rhabdomyolysis can occur. The body temperature decreases. The skeletal muscles relax; occasionally generalised seizures can develop, especially in children. Death may occur from respiratory failure. Death occurs mostly due to respiratory insufficiency or due to complications such as pulmonary oedema. Aspiration pneumonia can develop.

Therapy of intoxication

In unconscious patients with respiratory arrest ventilation, intubation, and intravenous administration of opioid antagonists (e. g. 0,4 mg naloxone intravenously) are indicated. In case of persistent respiratory insufficiency, the single dose has to be repeated 1 to 3 times in 3-minute intervals until the respiratory rate is back to normal and the patient responds to painful stimuli.

The patient must be strictly monitored (at least for 24 hours) since the duration of action of the opioid antagonist is shorter compared to that of morphine so that recurrence of the respiratory insufficiency has to be expected.

The single dose of the opioid antagonist is 0,01 mg per kg body weight in children. Additionally, measures to prevent a decrease in body temperature and to supplement volume may be necessary.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Opioids

ATC-code: N02A A01

Morphine is a phenanthrene alkaloid from *Papaver somniferum* with opioid-agonistic properties. It

shows distinct affinity to μ-receptors.

Central effects

Morphine has analgesic, antitussive, sedative, tranquilising, and antidiuretic effects. It provokes respiratory depression and miosis. Emetic and antiemetic effects have been described, the latter occurring as a delayed effect, furthermore a slight decrease in blood pressure and heart rate was reported.

Peripheral effects

Constipation, contraction of the sphincters of the bile ducts, increase in tone of the urinary bladder muscles and the vesical sphincter, prolonged stomach passage effected by pylorus constriction, flushing, urticaria and pruritus due to the release of histamine, and in asthmatic patients bronchospasm, influence on the hypophyseal-hypothalamic axis and consequently influence on hormone effects of corticoids, sex hormones, prolactin and antidiuretic hormone. Manifestation of clinical symptoms due to these hormonal changes may be feasible.

Onset of action after oral application is after 30-90 minutes. The duration of action lasts about 4-6 hours and markedly longer in prolonged-release formulations.
Onset of action after intramuscular or subcutaneous application is after 15-30 minutes, after intravenous application within a few minutes. Independent of these routes of administration the duration of action last about 4-6 hours.

In vitro as well as animal studies show different effects of opioids of natural origin such as morphine on components of the immune system. The clinical relevance of these findings is not known.

5.2 Pharmacokinetic properties

Following oral application morphine is absorbed with a T_{max} of 1.1 hours, primarily from the upper small intestine and to a minor extent also from the stomach. The low absolute bioavailability (20-40 %) is attributed to an extensive first-pass effect.

About 20-35 % of morphine is bound to plasma proteins, primarily to the albumin fraction.

After intravenous administration of 4-10 mg as a single dose the distribution volume of morphine is reported at 1,0 to 4,7 l/kg. High tissue concentrations are encountered in the liver, the kidneys, in the gastrointestinal tract and in muscles. Morphine crosses the blood brain barrier.

Metabolism of morphine occurs primarily in the liver but also in bowel epithelium. The main step is the glucuronidation of the phenolic hydroxyl moiety effected by the hepatic UDP-glucuronyl transferase and N-demethylation.

Main metabolites are morphine-3-glucuronide and to a minor extent morphine-6-glucuronide. Among other components sulphate conjugates and oxidative metabolites such as normorphine, morphine-N-oxide and a morphine derivative hydroxylised in position 2 are formed. The half-life of the glucuronides is markedly longer than that of morphine itself. Morphine-6-glucuronide is biologically active. A prolonged effect in patients with renal insufficiency may be attributable to this metabolite.

Following oral and parenteral application, about 80 % of the administered morphine is recovered in urine (10 % of unchanged morphine, 4 % of normorphine, and 65 % as glucuronides with a ratio of 10:1 for morphine-3-glucuronide: morphine-6-glucuronide). The elimination half-life of morphine is subject to high interindividual variability. Following parenteral application, it ranges from 1,7 to 4,5 hours on average, occasionally about 9 hours were reported. Approximately 10 % of the morphine glucuronides are excreted via the bile with the faeces.

5.3 Preclinical safety data

During continuous application of morphine, the sensitivity of the CNS towards morphine decreases. This habituation effect can be so marked that doses are tolerated which at a first application would be toxic due to respiratory depression. Due to the euphoric effect of morphine dependence can develop (see section 4.4).

Clearly positive findings on mutagenicity are available which indicate that morphine has a clastogenic

potential and does exert this effect on germ cells, too. For this reason, morphine must be regarded as a substance with mutagenic effect; it has to be assumed that this kind of effect occurs also in humans.

Morphine should be administered only if effective contraceptive measures are ensured.

Long-term studies in animals assessing a carcinogenic potential of morphine are not available.

Animal studies have revealed a damaging potential for the offspring during the entire duration of pregnancy (CNS malformation, growth retardation, testicular atrophy, changes concerning the neurotransmitter systems and behavioural changes, dependence). In male rats, reduced fertility and chromosomal damage in gametes have been reported. Furthermore, in several animal species morphine had an effect on the sexual performance of males and on the fertility of females.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium benzoate 1 mg/ml

Purified water

Citric acid

Sodium edetate (Ph. Eur.)

6.2 Incompatibilities

Not known.

6.3 Shelf life

The shelf life is 3 years. After opening of the bottle Oramorph® Oral Drops 20 mg/ml is stable for 90 days.

6.4 Special precautions for storage

Store at or below 25 °C. Store the bottle in the outer carton in order to protect from light.

6.5 Nature and contents of container

Container equipped with a dropping device containing 20 ml oral drops solution.

6.6 Special precaution for disposal

No special instructions.

7 HOLDER OF CERTIFICATE OF REGISTRATION

Eurolab (Pty) Ltd

Woodmead Office Park, 3 Stirrup Lane

Van Reenens Avenue, Woodmead, 2144

8 REGISTRATION NUMBER

To be allocated

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

To be allocated

10 DATE OF REVISION OF THE TEXT