

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Oramorph Concentrated oral solution 20 mg/ml

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Morphine sulfate 20mg per 1 ml.

Excipient(s) with known effect

Amaranth (E123) 0.03 mg per 1 ml and sodium benzoate (E211) 1.0 mg per 1 ml.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Oral solution.

A clear, red oral solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

For the relief of severe pain in adults, adolescents (aged 13-18 years) and children (aged 1-12 years).

4.2 Posology and method of administration

Posology

Adults: Recommended dose 10-20 mg (0.5 - 1.0 ml) every 4 hours.

Maximum daily dose: 120 mg per day.

Paediatric population:

Children 13-18 years: Recommended dose 5-20 mg (0.25 – 1.0 ml) every 4 hours

Maximum daily dose: 120 mg per day

Children 6-12 years: Recommended dose 5-10 mg (0.25-0.5 ml) every 4 hours

Maximum daily dose: 60 mg per day

Children 1-5 years: Recommended dose 5 mg (0.25 ml) every 4 hours.

Maximum daily dose: 30 mg per day

Children under 1 year: Not recommended.

Dosage can be increased under medical supervision according to the severity of the pain and the patient's previous history of analgesic requirements.

Special populations:

Reductions in dosage may be appropriate in the elderly and in patients with chronic hepatic disease (for acute hepatic disease see section 4.3), renal impairment, severe hypothyroidism, adrenocortical insufficiency, prostatic hypertrophy, shock or where sedation is undesirable.

Discontinuation of therapy

Prior to starting treatment with opioids, a discussion should be held with patients to put in place a strategy for ending treatment with Oramorph in order to minimise the risk of addiction and drug withdrawal syndrome (see section 4.4).

Method of Administration

For oral use

A graduated oral dosing syringe with adaptor is supplied with this dosage form and should be used for accurate and convenient dose adjustment. The required dose may be added to a soft drink immediately prior to administration. Patients should be advised that if they do this, they should swallow it immediately after mixing and not leave unattended.

Instructions for administration

The required dose should be measured using the enclosed graduated syringe and adaptor as described in the steps below: Open the bottle and put the adaptor onto the top of the open bottle neck by pressing. Make sure it is fixed well in place. Insert the syringe into the adaptor opening. Make sure the syringe is tightly inserted. Turn the bottle upside down and draw out the required amount of Oramorph Concentrated.

The adaptor should remain in the bottle after first use. The bottle cap should be replaced after use.

When patients are transferred from other morphine preparations to Oramorph preparations dosage titration may be appropriate.

Morphine sulfate is readily absorbed from the gastro-intestinal tract following oral administration. However, when oral Oramorph preparations are used in place of parenteral morphine, a 50 % to 100 % increase in dosage is usually required in order to achieve the same level of analgesia.

Treatment goals and discontinuation

Before initiating treatment with Oramorph, a treatment strategy including treatment duration and treatment goals, and a plan for end of the treatment, should be agreed together with the patient, in accordance with pain management guidelines. During treatment, there should be frequent contact between the physician and the patient to evaluate the need for continued treatment, consider discontinuation and to adjust dosages if needed. When a patient no longer requires therapy with Oramorph it may be advisable to taper the dose gradually to prevent symptoms of withdrawal. In absence of adequate pain control, the possibility of hyperalgesia, tolerance and progression of underlying disease should be considered (see section 4.4).

Duration of treatment

Oramorph should not be used longer than necessary.

4.3 Contraindications

- hypersensitivity to the active substance or to any of the excipients listed in section 6.1
- respiratory depression
- obstructive airways disease
- paralytic ileus (see section 4.4)
- acute hepatic disease
- acute alcoholism
- head injuries (see section 4.4)
- coma (see section 4.4)
- increased intracranial pressure (see section 4.4)
- convulsive disorders
- patients with known morphine sensitivity
- concurrent administration with monoamine oxidase inhibitors or within two weeks of discontinuation of their use (see section 4.5)
- patients with pheochromocytoma. Morphine and some other opioids can induce the release of endogenous histamine and thereby stimulate catecholamine release
- acute asthma exacerbations (see section 4.4 for information relating to use in controlled asthma)

4.4 Special warnings and precautions for use

Care should be exercised if morphine sulfate is given

- in the first 24 hours post-operatively,
- in hypothyroidism (see section 4.2),

- and where there is reduced respiratory function, such as kyphoscoliosis, emphysema, cor pulmonale and severe obesity. AsthmaIt has been suggested that opioids can be used with caution in controlled asthma. However, opioids are contraindicated in acute asthma exacerbations (see section 4.3). Head injury and increased intracranial pressureOramorph is contraindicated in patients with increased intracranial pressure, head injuries and coma (see section 4.3). The capacity of morphine to elevate cerebrospinal fluid pressure may be greatly increased in the presence of already elevated intracranial pressure produced by trauma. Also, morphine may produce confusion, miosis, vomiting and other adverse reactions which may obscure the clinical course of patients with head injury. Abdominal conditionsMorphine sulfate must not be given if paralytic ileus is likely to occur (see section 4.3), or if the patient has bowel or obstructive biliary disease. Should paralytic ileus be suspected or occur during use, Oramorph should be discontinued immediately. Caution should be exercised where there is an obstructive bowel disorder, biliary colic, operations on the biliary tract, acute pancreatitis or prostatic hyperplasia. If constipation occurs this may be treated with the appropriate laxatives. Care should be exercised in patients with inflammatory bowel disease. Morphine may obscure the diagnosis or clinical course of patients with acute abdominal conditions and complications following abdominal surgery. Hypotensive effectThe administration of morphine may result in severe hypotension in individuals whose ability to maintain homeostatic blood pressure has already been compromised by depleted blood volume or the concurrent administration of drugs such as phenothiazine or certain anaesthetics (see section 4.5). Drug dependence, tolerance and potential for abuseMorphine sulfate is an opioid agonist and controlled drug. For all patients, prolonged use of this product may lead to drug dependence (addiction), even at therapeutic doses. The risks are increased in individuals with current or past history of substance misuse disorder (including alcohol misuse) or mental health disorder (e.g., major depression). Additional support and monitoring may be necessary when prescribing for patients at risk of opioid misuse. A comprehensive patient history should be taken to document concomitant medications, including over-the-counter medicines and medicines obtained on-line, and past and present medical and psychiatric conditions. Patients may find that treatment is less effective with chronic use and express a need to increase the dose to obtain the same level of pain control as initially experienced. Patients may also supplement their treatment with additional pain relievers. These could be signs that the patient is developing tolerance. The risks of developing tolerance should be explained to the patient. Overuse or misuse may result in overdose and/or death. It is important that patients only use medicines that are prescribed for them at the dose they have been prescribed and do not give this medicine to anyone else. Morphine sulfate may be abused by inhaling or injecting the product. These practices pose a significant risk to the abuser that could result in overdose and death. Patients should be closely monitored for signs of misuse, abuse, or addiction. The clinical need for analgesic treatment should be reviewed regularly. Drug withdrawal syndromePrior to starting treatment with any opioids, a discussion should be held with patients to put in place a withdrawal strategy for ending treatment with Oramorph. Drug withdrawal syndrome may occur upon abrupt cessation of therapy or dose reduction. When a patient no longer requires therapy, it is advisable to taper the dose gradually to minimise symptoms of withdrawal. Tapering from a high dose may take weeks to months. The opioid drug withdrawal syndrome is characterised by some or all of the following: restlessness, lacrimation, rhinorrhoea, yawning, perspiration, chills, myalgia, mydriasis and palpitations. Other symptoms may also develop including irritability, agitation, anxiety, hyperkinesia, tremor, weakness, insomnia, anorexia, abdominal cramps, nausea, vomiting, diarrhoea, increased blood pressure, increased respiratory rate or heart rate. If women take this drug during pregnancy, there is a risk that their newborn infants will experience neonatal withdrawal syndrome. HyperalgesiaHyperalgesia may be diagnosed if the patient on long-term opioid therapy presents with increased pain. This might be qualitatively and anatomically distinct from pain related to disease progression or to breakthrough pain resulting from development of opioid tolerance. Pain associated with hyperalgesia tends to be more diffuse than the pre-existing pain and less defined in quality. Symptoms of hyperalgesia may resolve with a reduction of opioid dose. HypersensitivityHypersensitivity and anaphylactic reactions have both occurred with the use of Oramorph. Care should be taken to elicit any history of allergic reactions to opiates. Oramorph is contraindicated in patients known to be hypersensitive to morphine sulfate (see section 4.3).

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.

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 amenorrhoea.

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, morphine should 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 Oramorph.

Repeated use of Oramorph 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 Oramorph 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 Oramorph 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.

Risk in special populations

Morphine is metabolised by the liver and should be used with caution in patients with hepatic disease as oral bioavailability may be increased. It is wise to reduce dosage in chronic hepatic and renal disease, severe hypothyroidism, adrenocortical insufficiency, prostatic hypertrophy or shock (see section 4.2).

The active metabolite Morphine-6-glucuronide may accumulate in patients with renal failure, leading to CNS and respiratory depression.

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.

Concomitant use of sedative medicines

Concomitant use of Oramorph and sedative medicines such as benzodiazepines or related drugs may result in sedation, respiratory depression, coma and death.

Because of these risks, concomitant use of Oramorph and sedative medicines should be reserved for patients for whom alternative treatment options are not possible.

Oramorph particularly when prescribed concomitantly with sedative medicines, should be used at the lowest effective dose for the shortest period of time.

Patients should be monitored closely for signs and symptoms of respiratory depression and sedation (see also section 4.5).

Concomitant use of 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).

Excipient related warnings

Oramorph Concentrated Oral Solution contains the excipient Amaranth (E123), which may cause allergic reactions.

This medicine also contains 1 mg sodium benzoate (E211) in each 1 ml.

This medicine contains less than 1 mmol sodium (23 mg) per ml, that is to say essentially 'sodium free'.

4.5 Interaction with other medicinal products and other forms of interaction

Monoamine oxidase inhibitors

Monoamine oxidase inhibitors are known to interact with narcotic analgesics producing CNS excitation or depression with hyper- or hypotensive crisis, therefore their concomitant use with Oramorph is contraindicated (see section 4.3).

Gabapentin and Pregabalin

Morphine should be used with caution in patients who are concurrently receiving other central nervous system depressants including sedatives or hypnotics, general anaesthetics, phenothiazines, other tranquilisers, muscle relaxants, antihypertensives, gabapentin or pregabalin and alcohol. Interactive effects resulting in respiratory depression, hypotension, profound sedation, or coma may result if these drugs are taken in combination with the usual doses of morphine.

Ritonavir

Although there are no pharmacokinetic data available for concomitant use of ritonavir with morphine, ritonavir may increase the activity of glucuronyl transferases. Consequently, co-administration of ritonavir and morphine may result in decreased serum concentrations of morphine with possible loss of analgesic effectiveness.

Rifampicin

Rifampicin can reduce the serum concentration of morphine and decrease its analgesic effect, the mechanism of which is not known.

Cimetidine

Cimetidine inhibits the metabolism of morphine.

CNS depressants

It should be noted that morphine potentiates the effects of other CNS depressants such as tranquillisers, anaesthetics (see section 4.4), sedatives (e.g. benzodiazepines), antipsychotics, tricyclic antidepressants and alcohol, which might lead to respiratory depression, coma and death. The dose and duration of concomitant use should be limited (see section 4.4).

Esmolol

Morphine may increase plasma concentrations of esmolol.

Domperidone/metoclopramide

Opioid analgesics including morphine may antagonise the actions of domperidone and metoclopramide on gastro-intestinal activity.

Oral P2Y12 inhibitors

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.

Mexiletine

The absorption of mexiletine may be delayed by concurrent use of morphine.

Phenothiazine antiemetics

Phenothiazine antiemetics may be given with morphine. However, hypotensive effects have to be considered (see section 4.4).

4.6 Fertility, pregnancy and lactation

Pregnancy

Although morphine sulfate has been in general use for many years, there is inadequate evidence of safety in human pregnancy.

Morphine is known to cross the placenta. Therefore, Oramorph should not be used in pregnancy, especially the first trimester unless the expected benefit is thought to outweigh any possible risk to the foetus.

Regular use during pregnancy may cause drug dependence in the foetus, leading to withdrawal symptoms in the neonate.

If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available.

Administration during labour may depress respiration in the neonate and an antidote for the child should be readily available.

The risk of gastric stasis and inhalation pneumonia is increased in the mother during labour. Since morphine rapidly crosses the placental barrier it should not be used during the second stage of labour or in premature delivery because of the risk of secondary respiratory depression in the newborn infant.

Breast-feeding

Although morphine sulfate has been in general use for many years, there is inadequate evidence of safety during lactation.

Administration to nursing women is not recommended as morphine sulphate may be secreted in breast milk and may cause respiratory depression in the infant.

Fertility

Long term use of opioid analgesics can cause hypogonadism and adrenal insufficiency in both men and women. This is thought to be dose related and can lead to amenorrhoea, reduced libido, infertility and erectile dysfunction.

Animal studies have shown that morphine may reduce fertility (see 5.3. preclinical safety data).

4.7 Effects on ability to drive and use machines

Morphine sulfate is likely to impair ability to drive and to use machinery. This effect is even more enhanced when used in combination with alcohol or CNS depressants.

Patients should be warned not to drive or operate dangerous machinery after taking Oramorph.

4.8 Undesirable effects

In normal doses, the commonest side effects of morphine sulfate 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.

Data from clinical trials are not available. Therefore it is not possible to provide information on the frequencies of undesirable effects, except where stated. A full list of currently known adverse reactions is presented below:

SOC Category	Side effect
<i>Immune system disorders</i>	Hypersensitivity Anaphylactic reaction (see section 4.4) Anaphylactoid reactions
<i>Psychiatric disorders</i>	Confusional state Restlessness Altered mood Hallucination Dependence (see section 4.4)
<i>Nervous system disorders</i>	Somnolence Headache Increased intracranial pressure (see section 4.4) Allodynia Hyperalgesia (see section 4.4)
<i>Eye Disorders</i>	Miosis
<i>Ear and labyrinth disorders</i>	Vertigo

<i>Respiratory, thoracic and mediastinal disorders</i>	Respiratory depression (see section 4.4 and section 4.6) Central sleep apnoea syndrome
<i>Cardiac disorders</i>	Bradycardia Tachycardia Palpitations
<i>Vascular disorders</i>	Hypotension Flushing
<i>Gastrointestinal disorders</i>	Nausea Vomiting Constipation (see section 4.4) Dry mouth Pancreatitis
<i>General disorders and administration site conditions</i>	Hypothermia Drug tolerance (see section 4.4) Drug withdrawal syndrome* (see section 4.4 and section 4.6)
<i>Hepatobiliary Disorders</i>	Biliary colic Spasm of sphincter of Oddi
<i>Skin and subcutaneous tissue disorders</i>	Urticaria Pruritus Hyperhidrosis Acute generalised exanthematous pustulosis (AGEP)
<i>Musculoskeletal and connective tissue disorders</i>	Muscle rigidity
<i>Renal and urinary disorders</i>	Dysuria Ureteral spasm Oliguria
<i>Reproductive system and breast disorders</i>	Decreased libido Erectile dysfunction

*Frequency uncommon ($\geq 1/1,000$ to $< 1/100$)

Drug dependence

Repeated use of Oramorph 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

Patients should be informed of the signs and symptoms of overdose and to ensure that family and friends are also aware of these signs and to seek immediate medical help if they occur.

Symptoms

Signs of morphine toxicity and overdosage are likely to consist of pin-point pupils, respiratory depression and hypotension. Circulatory failure, pneumonia aspiration and deepening coma may occur in more severe cases. Convulsions may occur in infants and children. Death may occur from respiratory failure.

Treatment

Adults: Administer 0.4-2 mg of naloxone intravenously. Repeat at 2-3 minute intervals as necessary to a maximum of 10 mg, or by 2 mg in 500 ml of normal saline or 5 % dextrose (4 micrograms/ml). Children: 5-10 micrograms per kilogram body weight intravenously. If this does not result in the desired degree of clinical improvement, a subsequent dose of 100 mcg/kg body weight may be administered.

Care should always be taken to ensure that the airway is maintained. Assist respiration if necessary. Maintain fluid and electrolyte levels. Oxygen, i.v. fluids, vasopressors and other supportive measures should be employed as indicated. Peak plasma concentrations of morphine are expected to occur within 15 minutes of oral ingestion. Therefore gastric lavage and activated charcoal are unlikely to be beneficial.

Caution: the duration of the effect of naloxone (2-3 hours) may be shorter than the duration of the effect of the morphine overdose. It is recommended that a patient who has regained consciousness after naloxone treatment should be observed for at least 6 hours after the last dose of naloxone.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Natural opium alkaloids. ATC code: NO2AA01

Morphine binds to specific receptors which are located at various levels of the central nervous system and also in various peripheral organs. The pain sensation and the affective reaction to pain is relieved by interaction with the receptors in the central nervous system.

5.2 Pharmacokinetic properties

Absorption

Morphine sulfate is readily absorbed from the gastrointestinal tract following oral administration. Following oral administration of radiolabelled morphine sulfate to humans, peak plasma levels were reached after approximately 15 minutes. Morphine undergoes significant first pass metabolism in the liver resulting in a systemic bioavailability of approximately 25% (range 15-49%).

Distribution

Morphine is distributed throughout the body but found mainly in the kidneys, liver, lung and spleen with lower concentrations being found in the brain and muscles. Approximately one third of morphine in the plasma is protein bound after a therapeutic dose. Morphine diffuses across the placenta and traces of the drug appear in breast milk.

Biotransformation

Metabolism of morphine principally involves conjugation to morphine 3- and 6- glucuronides. Small amounts are also metabolised by N-demethylation and O-methylation. Morphine-6-glucuronide has pharmacological effects indistinguishable from those of morphine. The half-life of morphine is approximately 2 hours. The half-life of morphine-6-glucuronide is somewhat longer.

Elimination

About 10 % of a dose of morphine is excreted through the bowel into the faeces. The remainder is excreted in the urine, mainly in the form of conjugates. About 90 % of a single dose of morphine is excreted in 24 hours. Enterohepatic circulation of morphine and its metabolites can occur, and may result in small quantities of morphine being present in the urine or faeces several days after the last dose.

5.3 Preclinical safety data

In male rats, reduced fertility and chromosomal damage in gametes have been reported.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Disodium Edetate
Sodium Benzoate (E211)
Anhydrous Citric Acid
Amaranth (E123)
Purified Water

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Unopened: 3 years.

Opened: 4 months after first opening

6.4 Special precautions for storage

Do not store above 25°C. Store in the original container in order to protect from light.

6.5 Nature and contents of container

Type III amber glass bottles containing 30 ml or 120 ml morphine sulfate 20 mg/ml solution. The bottle is fitted with a tamper-evident child-resistant closure with an outer overcap of polypropylene and expanded PE liner.

A graduated oral dosing syringe (HDPE inner piston/plunger and polypropylene outer barrel) and LDPE adaptor is enclosed in the carton with each bottle.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Glenwood GmbH
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Arabellastr. 17
81925 Munich
Germany

8 MARKETING AUTHORISATION NUMBER

PA2256/004/002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

January 2024