SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Oramorph Syrup 2 mg/ml

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml syrup contains:

Morphine sulfate pentahydrate	2 mg

Excipients with known effect:

Methyl parahydroxybenzoate	1.8 mg/ml
Propyl parahydroxybenzoate	0.2 mg/ml
Ethanol (alcohol)	0.105 ml/ml
Glucose liquid	100 mg/ml
Sucrose	300 mg/ml

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Syrup

Nearly colourless syrupy solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Oramorph is indicated for the symptomatic relief of severe chronic pain.

4.2 Posology and method of administration

Posology

The Oramorph dose is adjusted depending on the severity of pain and with regards to the individual sensitivity of the patient.

Under medical control the dose can be increased depending on the severity of pain and depending on the use of analgesics so far.

For oral use.

The solution should be administered with some liquid (water or juice).

The recommended dose depends on the individual pain condition and is for

Adults: initial dose usually 10-30 mg morphine sulfate pentahydrate (corresponding to 5-15 ml Oramorph 2 mg/ml - syrup) every 4-6 hours.

Immediately prior to administration the prescribed Oramorph dose is measured with the aid of the provided measuring pipette of 5 ml, graduated with marks on every 0.25 ml.

Elderly patients:
In elderly patients or in patients that should not experience sedation the dosage should be reduced. Older patients (usually 75 years and older) and patients with poor overall physical condition may be sensitive to morphine. Therefore, the adjustment of dose has to be done more carefully and / or the dosage intervals have to be extended. As appropriate, lower dosage strengths have to be given instead.

Patients with impaired liver and/or kidney function:
In patients with liver and/or kidney dysfunction and if a delayed gastrointestinal passage is suspected Oramorph should be dosed especially carefully.

Discontinuation of therapy:
An abstinence syndrome may be precipitated if opioid administration is suddenly discontinued. Therefore the dose should be gradually reduced prior to discontinuation.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Diarrhoea caused by poisoning.
- Acute respiratory insufficiency or respiratory depression, obstructive airways disease.
- Concurrent administration with monoamine oxidase (MAO) inhibitors or within 2 weeks of Discontinuation of treatment with MAO (see section 4.5).

The risk-benefit of morphine use should be evaluated when the following medical problems are present:
- Acute abdomen.
- Asthma attacks and acute and severe bronchial obstruction.
- Cardiac arrhythmias.
- History of convulsions (see Sect. 4.4).
- Acute alcohol intoxication.
- Agitation in patients secondary to use of alcohol or hypnotics, emotional instability, suicidal ideation.
- Head injury and conditions with increased intracranial pressure.
- Acute liver disorders (hepatitis, hepatic porphyria).
- Paralytic ileus.
- Coma.
- Patients with phaeochromocytoma. Morphine and some other opioids can induce the release of endogenous histamine and thereby stimulate catecholamine release.
- Pregnancy and lactation (see section 4.6).

4.4 Special warnings and precautions for use

This medicine should be used carefully in the following conditions:

– In patients with obstructive respiratory disorders, reduced respiratory reserve (e. g. kyphoscoliosis, emphysema or severe adiposis), anoxia, hypercapnia, respiratory insufficiency (patients may become comatose because of carbon dioxide retention), pulmonary disorders
– Cor pulmonale
– Impaired consciousness, shock, CNS depression

- Known opioid dependency. Patients dependent on opioids may be prescribed with morphine if this appears essential for the treatment of pain, particularly in case of acute conditions. Special monitoring of treatment is recommended
- Within the first 24 hours post-surgery
- Hypovolemia
- In patients with chronic kidney or liver disorders, pancreatitis, myxoedema, adrenocortical insufficiency, hypothyroidism, pheochromocytoma, prostatic hypertrophy with residual urine (risk of bladder rupture secondary to urinary retention)
- Fulminant ulcerative colitis
- In patients with obstructive bile or urinary tract diseases or spasms of bile ducts and urinary tract secondary to stone formation, since morphine may worsen these symptoms
- After surgery affecting the biliary system, since morphine may cause abdominal pain
- Epilepsy or increased propensity to seizures. Morphine lowers the threshold for onset of epileptic syndromes. Morphine should be administered under strict medical control in patients suffering from epilepsy and the dosage should be adjusted individually

Abdominal conditions

Morphine sulfate pentahydrate 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 effect

The 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). Careful dosing is needed in elderly patients, patients with heart insufficiency and with impaired liver or kidney function, respectively (dose reduction if needed).

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 drug is used, and with higher doses. Symptoms can be minimised with adjustments of dose or dosage form, and gradual withdrawal of morphine. For individual symptoms, see section 4.8.

Tolerance to the analgesic, respiratory depressant, sedative and euphoric effects of morphine usually develops on long-term use. However, tolerance to all side effects does not develop at an equal rate; therefore, muscle twitching, tremor, mental confusion, hallucinations and convulsions can occur. Cross-tolerances with other opioids occur.

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 cortisol concentration should be monitored and if needed 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.

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 drugs

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 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 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 (see section 4.5).

Oral P2Y12 inhibitor antiplatelet therapy

Within the first day of concomitant P2Y12 inhibitor (e.g. clopidogrel, prasugrel, ticagrelor) and morphine treatment, reduced efficacy of P2Y12 inhibitor treatment has been observed (see section 4.5).

Interference with diagnostic tests

Morphine interferes with the diagnostic determination of cerebrospinal fluid pressure, the concentrations of plasma amylase, plasma lipase, serum alanine aminotransferase (SGPT), serum aspartate aminotransferase (SGOT), serum bilirubin and serum alkaline phosphatase.

Excipients related warnings

Methyl parahydroxybenzoate and propyl parahydroxybenzoate can cause allergic reactions (also delayed hypersensitivity reactions).

This medicine contains 0.105 ml alcohol (ethanol) per ml solution which is equivalent to about 10% v/v, and it must not be given to patients suffering from alcoholism. The alcohol content needs to be considered in patients with higher risk due to liver disease.

This medicine contains 100 mg glucose liquid per ml solution. Patients with the rare glucose-galactose malabsorption should not take this medicine.

This medicine contains 300 mg sucrose per ml solution. Patients with rare hereditary conditions of fructose/galactose intolerance, glucose-galactose malabsorption or sucrase isomaltase insufficiency should not take this medicine.

Note for diabetic patients:
5 ml solution corresponds to 0.17 bread exchange.

4.5 Interaction with other medicinal products and other forms of interaction

Sedative medicines such as benzodiazepines or related drugs
The concomitant use of opioids with sedative medicines such as benzodiazepines or related drugs 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).

Other CNS depressants
The concomitant application of tranquilisers, anaesthetics (see Section 4.4), hypnotics, sedatives, tricyclic antidepressants, antipsychotics, sedating H1 antihistamines (e.g. hydroxyzine), or alcohol increases the CNS depressing effect of morphine, especially the depressive effect on respiration. Death may occur. If used concurrently with CNS depressants, dosage adjustment may be required.

Phenothiazines
Phenothiazine antiemetics may be given with morphine. However phenothiazines may augment respiratory depression and may increase risk of hypotension as additive hypotensive effects may occur (see Section 4.4). Concurrent use of phenothiazines may enhance sedative effects, but at the same time, some phenothiazines (promethazine) have an antianalgesic effect.

Oral Anticoagulants
Morphine may enhance response to anticoagulants such as warfarin (coumadin); however, short-term use does not likely have a significant effect.
A delayed and decreased exposure to oral P2Y12 inhibitor antiplatelet therapy (e.g. clopidogrel, prasugrel, ticagrelor) 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.

Medicines with anticholinergic effect
Antihistamines, antiemetics, antimuscarinics (e.g. drugs for treatment of Morbus Parkinson) can enhance anticholinergic side effects of opioids and may result in increased risk of severe constipation and/or urinary retention.

Monoamine oxidase inhibitors
If monoamine oxidase inhibitors are used within 14 days prior to the initiation of morphine or these are administered concomitantly with morphine life-threatening effects on the central nervous system, respiration or circulation can occur (see section 4.3).

Cimetidine
Cimetidine inhibits morphine metabolism.

Skeletal Muscle Relaxants
Morphine can enhance the effect of muscle relaxants.

Rifampicin
Rifampicin can reduce the plasma concentration of morphine and decrease its analgesic effect (see section 4.4).

Levallorphan/Naloxone
Antagonise the analgesic, CNS and respiratory depressant effects of opioid analgesics and may precipitate withdrawal symptoms in physically dependent patients: dosage of levallophan or naloxone should be carefully titrated when used to treat opioid overdosage in dependent patients.

Methadone or Opioid Agonist Analgesics
Additive CNS depressant, respiratory depressant and hypotensive effects may occur if two or more opioid agonist analgesics are used concomitantly.

Neuromuscular Blocking Agents
Respiratory depressant effects of neuromuscular blocking agents may be additive to central respiratory depressant effects of opioid analgesics; caution is recommended when an opioid drug is administered during surgery or in the immediate post-operative period to a patient who has received a neuromuscular blocking agent.

4.6 Fertility, pregnancy and lactation

Pregnancy
Morphine must not be used during pregnancy since preclinical studies indicated damages to the offspring (see section 4.3). The use of morphine during labour is not recommended due to the risk of respiratory depression in the newborn infant.
Newborns whose mothers received opioid analgesics during pregnancy should be monitored for signs of neonatal withdrawal (abstinence) syndrome. Treatment may include an opioid and supportive care.

Lactation
The maternal use during lactation is not recommended since morphine is excreted in the breast milk. Withdrawal symptoms can be observed in newborn infants if mothers are exposed to a chronic treatment. Therefore, weaning is necessary prior to the administration of Oramorph (see section 4.3).

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

4.7 Effects on ability to drive and use machines

Even if the recommendations for use are adhered to morphine sulfate pentahydrate can have an impact on 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 and centrally depressing substances.

4.8 Undesirable effects

The incidence of the undesirable effects is classified as follows:

Very common	(≥ 1/10)
Common	(≥ 1/100 to < 1/10)
Uncommon	(≥ 1/1000 to < 1/100)
Rare	(≥ 1/10.000 to < 1/1000)
Very rare	(< 1/10.000)
Not known	cannot be estimated from the available data

Immune system disorders
Rare: anaphylactic and anaphylactoid reactions, onset of asthma in sensitive patients.

Respiratory, thoracic and mediastinal disorders
Uncommon: respiratory depression, bronchospasm
Very rare: dyspnoea
Non-cardiogenic pulmonary oedema have been reported in patients treated under intensive-care conditions.

Endocrine disorders
Rare: shiver, hypothermia, increased intracranial pressure
Very rare: syndrome of inadequate ADH secretion (SIADH, with hyponatraemia as the main symptom)

Nervous system disorder
Common: dizziness, headache
Uncommon: disorientation, agitation, sedation, mood variability, somnolence, feeling of dizziness
Very rare: tremor, involuntary muscle twitching, epileptic seizures
Not known: allodynia, hyperalgesia (see section 4.4), hyperhidrosis

Psychiatric disorders
Morphine shows various psychiatric undesirable effects which with regard to severity and nature present differently in the individual patients (depending on the personality and duration of therapy).
Very common: mood changes, mostly euphoria, but also dysphoria
Common: changes in activity (mostly sedation, but also enhanced activity or agitation), insomnia and alterations of cognitive and sensory functions (e. g. disturbances in thinking, altered apprehensiveness/hallucinations, confusion)
Very rare: dependence (see section 4.4), decreased libido or impaired potency

Eye disorders
Common: miosis
Rare: blurred vision, diplopia and nystagmus
Miosis is a typical accompanying symptom.

Cardiac disorders
Uncommon: palpitation, flush (face)
Rare: decreased blood pressure, bradycardia, tachycardia, generalised asthenia up to syncope and cardiac insufficiency

Gastrointestinal disorders
Common: nausea, vomiting (especially at the beginning of therapy), constipation, anorexia, dyspepsia and taste alterations
Uncommon: dry mouth, colic
Rare: elevation of pancreatic enzymes, pancreatitis
Very rare: ileus, abdominal pain.

To avoid nausea and vomiting morphine can be administered together with an antiemetic. Obstipation can be treated with a laxative.

Hepatobiliary disorders
Uncommon: biliary spasm
Very rare: elevation of liver-specific enzymes

Skin and subcutaneous tissue disorders
Common: sweating, hypersensitivity reactions such as urticaria, pruritus
Very rare: other skin reactions such as exanthema and peripheral oedema (reversible upon termination of therapy). Morphine releases histamine and consequently can cause urticaria, other skin reactions and pruritus.

Musculoskeletal and connective tissue disorders
Very rare: muscle cramps, muscle rigidity

Renal and urinary disorders
Uncommon: urinary retention, antidiuretic effect, ureter spasm

Reproductive system and breast disorders:
Reduced libido or potency

General disorders and administration site conditions
Not known: drug withdrawal (abstinence) syndrome

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 section 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.

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 the national reporting system.

4.9 Overdose

Symptoms:
Symptoms of morphine intoxication and overdose respectively are respiratory depression, pneumonia aspiration, miosis (pinpoint pupils) and hypotension. In case of marked hypoxia the pupils are dilated, respiration is markedly reduced (breath rate of 2-4 per minute), the patient becomes cyanotic.
In more serious cases circulatory failure and deep coma can occur.
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 or due to complications such as pulmonary oedema.

Treatment:
Primarily clearing of airways and keeping them free as well as assisted or controlled ventilation are indicated.
In case of substantial overdose intravenous administration of 0.4-0.8 mg naloxone is recommended. If needed, administration can be repeated in 2-3 minutes intervals or it can be replaced with infusion of 2 mg in 500 ml saline solution or 5% dextrose solution (0.004 mg/ml). The infusion rate depends on the

doses administered before and it should be adjusted to the reaction of the patient. Since the naloxone effect fades after a relatively short period of time (2-3 hours) the patient needs to be monitored closely until respiration is reliably back to normal.

If morphine overdose does not cause significant clinical respiratory or circulatory depressions naloxone should not be administered. Naloxone must be administered with utmost caution to subjects with known or suspected physical dependence on morphine. In these cases sudden or complete antagonisation of opioid effects can cause acute withdrawal symptoms.

Further supporting measures (administration of oxygen, vasopressor agents, i. v. volume supplementation) are depending on the patient's condition.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties

Pharmacotherapeutic group: Analgesics, opioids, natural opium alkaloids, morphine
ATC-Code: N02AA01

Morphine binds to specific receptors located in the CNS and in various peripheral organs. Pain sensation and affective reaction to the pain is reduced by interaction with CNS receptors.

5.2 Pharmacokinetic Properties

Absorption:
Following oral application morphine sulfate pentahydrate is absorbed rapidly from the gastrointestinal tract.
Two thirds of an oral dose is absorbed with the maximum analgesic effect occurring after 60 minutes. However, the effect of a given dose is variable. The time curve is often long by the oral route and peak plasma levels are reached after approximately 2-3 hour following application of morphine solution with large inter-subject variability.

Distribution and biotransformation:
Morphine crosses the blood brain barrier but distributes into all tissues..
Metabolism occurs in the bowel and in the liver leading to the formation of morphine glucuronides with morphine-6-glucuronide probably being pharmacologically active.

Elimination:
About 10% of a dose of morphine is excreted through the bile in to the faeces. The remainder as conjugates or free morphine is excreted via glomerular filtration in the urine. Small quantities are excreted in breast milk and sweat.
About 90% of a single dose of morphine is excreted in 24 hours with traces up to 48 hours.

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

Methyl parahydroxybenzoate
Propyl parahydroxybenzoate
Sucrose

Glucose liquid
Ethanol (corresponding to 10 vol% alcohol)
Purified water

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months

The solution should be used within 1 month of first opening.

6.4 Special precautions for storage

Store the bottle in the outer carton in order to protect from light.
Store at or below 30°C

6.5 Nature and contents of container

Amber coloured glass bottle containing 100 ml drug product.
A plastic pipette of 5 ml, graduated with marks on every 0.25 ml is provided for measuring of the dose.

6.6 Special precautions for disposal and other handling

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Medicell Pharmaceutical (S) Pte Ltd
12 Tannery Road
#03-02/03 HB Centre 1
Singapore 347722

8. MARKETING AUTHORISATION NUMBER

SIN16036P

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

30 October 2020

10. DATE OF REVISION OF THE TEXT

October 2022