

# ORAMORPH® 20 MG/ML SOLUTION

## SUMMARY OF PRODUCT CHARACTERISTICS

### 1. NAME OF THE MEDICINAL PRODUCT

Oramorph® 20 mg/ml solution

### 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active pharmaceutical ingredient: Morphine sulphate .

1 ml oral drops, solution contains 20 mg morphine sulphate, corresponding to 15 mg morphine.  
For a full list of excipients, see section 6.1.

### 3. PHARMACEUTICAL FORM

Oral drops, solution  
Clear, colourless solution.

### 4. CLINICAL PARTICULARS

#### 4.1 Therapeutic indications

For the relief of moderate to severe pain

#### 4.2 Posology and method of administration

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

The recommended range of the single and daily doses for children and adults is stated in the following table based on a single dose of 0.2 to 0.3 mg morphine sulphate/kg body weight.

Age (body weight)	Single dose
Children under 3 years	contra indicated
Children 3-5 years (12.5 - 18 kg)	0.125-0.25 ml, i. e. 2-4 drops Oramorph® 20 mg/ml solution, corresponding to 2.5-5 mg morphine sulphate, every 4-6 hours
Children 6-12 years (20 - 40 kg)	0.25-0.5 ml, i. e. 4-8 drops Oramorph® 20 mg/ml solution, corresponding to 5-10 mg morphine sulphate, every 4-6 hours
Adolescents 13-18 years / Adults (40-50 kg)	0.5-1.0 ml, i. e. 8-16 drops Oramorph® 20 mg/ml solution, corresponding to 10-20 mg morphine sulphate, every 4-6 hours
Adults	0.5-3 ml, i. e. 8-48 drops Oramorph® 20 mg/ml solution, corresponding to 10-60 mg morphine sulphate, every 4-6 hours

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 needed other appropriate dosage strengths have to be considered alternatively or in combination with Oramorph® 20 mg/ml solution.

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

A calibrated oral dosing pipette is supplied with this dosage form for accurate and convenient dose adjustment. The required dose may be added to a soft drink immediately prior to administration.

Morphine Sulphate is readily absorbed from the gastro-intestinal tract following oral administration. However, when Oramorph oral solution is 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.

#### *Renal or hepatic impairment*

In patients with impaired liver or kidney function and in those with suspected delayed gastrointestinal passage Oramorph® 20 mg/ml solution 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 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.

#### *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 and duration of administration*

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

The physician decides about the duration of the treatment in dependence on the pain.

By no means Oramorph® 20 mg/ml solution should be given longer than absolutely necessary.

If prolonged analgesic treatment with Oramorph® 20 mg/ml solution 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® 20 mg/ml solution must not be administered in case of:

- hypersensitivity to morphine or to any of the excipients of Oramorph® 20 mg/ml solution
- paralytic ileus
- acute abdomen.
- respiratory depression
- obstructive airways disease
- head injuries
- delayed gastric emptying
- acute hepatic disease
- Acute alcoholism
- Coma
- Convulsive disorders
- Raised intracranial pressure
- concurrent administration of mono amine oxidase inhibitors or within two weeks of discontinuation of their use.
  
- Morphine and some other opioids can induce the release of endogenous histamine and thereby stimulate catecholamine release making them unsuitable for use in patients with phaeochromocytoma.
- Opioids are contra-indicated in acute asthma exacerbations, see section 4.4 for information relating to use in controlled asthma.
- Pregnancy and lactation

### 4.4 Special warnings and precautions for use

Especially careful monitoring by the physician and possibly dose reduction is needed in case of:

- opioid dependence
- disturbances of consciousness
- conditions associated with a disturbance of the respiratory centre and of the respiratory function or where there is reduced respiratory reserve (such as kyphoscoliosis, emphysema and severe obesity)
- 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 (paralytic ileus)
- chronic hepatic and renal disease
- myxoedema
- adrenocortical insufficiency
- phaeochromocytoma
- pancreatitis
- hypothyroidism
- epilepsy or increased propensity to seizures.

In case of an opioid overdose respiratory depression is the most important risk.

The use of morphine can be associated with physical dependence. Abrupt discontinuation after repeated use or application of an opioid antagonist can provoke typical signs of withdrawal (withdrawal syndrome).

*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

When a patient no longer requires therapy with morphine, it may be advisable to taper the dose gradually to prevent symptoms of withdrawal.

Therapeutic administration in patients with chronic pain is associated with a markedly reduced risk of psychological dependence and has to be assessed in a different light.

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.

Compared to patients not undergoing surgery the use of Oramorph® 20 mg/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 intraabdominal 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.

Oramorph® 20 mg/ml solution must not be used in children under 3 years of age.

*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

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.

Hypersensitivity and anaphylactic reaction have both occurred with the use of Oramorph. Care should be taken to elicit any history of allergic reactions to opiates.

Oramorph® 20 mg/ml solution must not be used in children under 3 years of age.

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 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® 20 mg/ml solution 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® 20 mg/ml solution 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).

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.

*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).

The use of Oramorph® 20 mg/ml solution can lead to positive results of doping tests.

#### **4.5 Interaction with other medicinal products and other forms of interaction**

The following interactions of this medicinal product have to be considered:

Concomitant application of morphine and other medicines with centrally sedating effects such as tranquilisers, anaesthetics, hypnotics and sedatives, neuroleptics, barbiturates, tricyclic antidepressants, antihistamines / 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 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).

Morphine may possibly increase plasma concentrations of esmolol.

Interactions have been reported in those subjects taking Oramorph and voriconazole. Interactions have been reported in those taking Oramorph and gabapentin. Both interactions suggest an increase in opioid adverse events when co-prescribed, the mechanism of which is not known. Caution should be taken where these medicines are co-prescribed.

In a study involving healthy volunteers (N=12), when a 60 mg controlled-release morphine capsule was administered 2 hours prior to a 600 mg gabapentin capsule, mean gabapentin AUC increased by 44% compared to gabapentin administered without morphine. Therefore, patients should be carefully observed for signs of CNS depression, such as somnolence, and the dose of gabapentin or morphine should be reduced appropriately.

Mixed agonist/antagonist opioid analgesics (e.g. buprenorphine, nalbuphine, pentazocine) should not be administered to a patient who has received a course of therapy with a pure opioid agonist analgesic.

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

Cimetidine and other drugs impairing liver metabolism can lead to higher morphine plasma concentrations due to the inhibition of its metabolism. Opioid analgesics including morphine may antagonise the actions of domperidone and metoclopramide on gastro-intestinal activity.

Concomitant use of ritonavir should be avoided as the plasma concentration of morphine may be increased.

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

Monoamine oxidase inhibitors are known to interact with narcotic analgesics producing CNS excitation or depression with hyper- or hypotensive crisis, (see section 4.3).

Morphine can enhance the effect of muscle relaxants.

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.

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

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.

## **4.6 Fertility, pregnancy and lactation**

### ***Pregnancy***

Data in humans are not sufficient to permit the assessment of a potential teratogenic risk. A potential correlation with a higher incidence of hernias was reported.

Morphine crosses the placental barrier. Animal studies have revealed a damaging potential for the off-spring during the entire duration of pregnancy (see section 5.3). Therefore, morphine may be used during pregnancy only if the benefit for the mother clearly outweighs the risk for the foetus.

Due to its mutagenic properties, morphine should only be used in males with procreative potential and females with childbearing potential if effective contraception is guaranteed.

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.

Withdrawal symptoms have been reported in neonates following prolonged morphine application during pregnancy.

### ***Delivery***

Morphine can prolong or shorten the duration of labour pains. Neonates of mothers receiving opioid analgesics during delivery should be monitored with regard to signs of respiratory depression or of withdrawal syndrome; if necessary, a specific opioid antagonist should be given.

### ***Lactation***

Morphine is excreted in human milk where concentrations higher than in maternal plasma are reached. Since clinically relevant concentrations can be reached in infants breast feeding is discouraged.

### ***Fertility***

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 can impair the attentiveness and the capability to react to such an extent that the ability to drive or to use machines is impaired or inexistent.

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 has to be done by the treating physician. During a stable therapeutic regimen driving is not prohibited generally.

## **4.8 Undesirable effects**

In normal doses, the commonest side effects of morphine are nausea, vomiting, constipation and drowsiness and confusion. With chronic therapy, nausea and vomiting are unusual but should they occur the morphine dosage can be readily combined with an anti-emetic if required. Constipation may be treated with appropriate laxatives.

For the evaluation of undesirable effects the following incidences are defined:

Very common	≥ 1/10
Common	≥ 1/100 to < 1/10
Uncommon	≥ 1/1000 to < 1/100
Rare	≥ 1/10000 to < 1/1000
Very rare	< 1/10000
Not known	Can't be estimated from the available data

Category	Very	Common	Uncommon	Not known
Immune system disorders			Allergic reaction	Anaphylactic reaction Anaphylactoid reaction
Psychiatric disorders Morphine shows various psychiatric undesirable effects which with regard to severity and nature present differently (depending on the personality and duration of therapy).	Very common: mood changes, mostly euphoria, but also dysphoria	<del>Confusion</del> <del>Insomnia</del> Common: changes in activity (mostly sedation, but also enhanced activity or agitation), insomnia, alterations of cognitive and sensory functions (e. g. disturbances in thinking, altered apprehensiveness/hallucinations, confusion)	Agitation Euphoria Hallucinations Mood altered  Very rare:dependence (see section 4.4), decreased libido and impaired potency	Drug dependence  Dysphoria  Thinking disturbances



Nervous system disorders - Depending on the dose, morphine leads to various extents of respiratory depression and sedation ranging from slight fatigue to giddiness.		Dizziness Headache Involuntary muscle contractions Somnolence	Convulsions Hypertonia Myoclonus Paraesthesia Syncope Very rare:tremor, involuntary muscle twitching, epileptic seizures	Hyperalgesia (see section 4.4) Not known: hyperhidrosis 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).
Eye disorders			Visual disturbance Very rare: blurred vision, diplopia, nystagmus	Miosis, Miosis is a typical accompanying symptom
Ear and labyrinth disorders			Vertigo	
Cardiac disorders			Palpitations, Heart failure	Uncommon: clinically relevant decrease or increase in blood pressure and heart rate Facial flushing, palpitations, generalised weakness up to loss of consciousness and heart failure can occur. Bradycardia Tachycardia
Vascular disorders			Facial flushing Hypotension	Hypertension

Respiratory thoracic and mediastinal disorders			Bronchospasm  Pulmonary oedema  Respiratory depression  Very rare: dyspnoea Non-cardiogenic pulmonary oedemas have been reported in patients treated under intensive-care conditions.	Cough decreased
Gastrointestinal disorders Depending on the dose, nausea and dry mouth can occur. Obstipation is a typical accompanying symptom of long-term treatment.	Constipation  Nausea	Abdominal pain Anorexia Dry mouth Vomiting Common: vomiting (especially at the beginning of therapy), anorexia, dyspepsia and taste alterations	Dyspepsia  Ileus  Taste perversion Rare: elevation of pancreatic enzymes and pancreatitis respectively	Very rare: ileus, abdominal pain
Hepatobiliary disorders			Increased hepatic enzymes Rare: biliary colics	Biliary pain Exacerbation of pancreatitis  Very rare: elevation of liver-specific enzymes
Skin and subcutaneous tissue disorders		Hyperhidrosis  Rash  Common: sweating, hypersensitivity reactions such as urticaria, pruritus	Urticaria  Very rare: other skin reactions such as exanthema and peripheral oedema (reversible upon termination of therapy) Anaphylactic and anaphylactoid reactions can occur.	
Renal and urinary disorders		Common: disturbances of micturition	Urinary retention Rare: renal colic	Ureteric spasm

Reproductive system and breast disorders				Amenorrhoea Decreased libido Erectile dysfunction
General disorders and administration site conditions		Asthenic conditions  Pruritus	Peripheral oedema	Tolerance can develop.  Rare: drug withdrawal (abstinence) syndrome Very rare: asthenia, malaise, chills, amenorrhoea
Musculoskeletal and connective tissue disorders				Very rare: muscle cramps, muscle rigidity
Endocrine disorders				Very rare: syndrome of inadequate ADH secretion (SIADH, with hyponatraemia as the main symptom).

Very rare: Diplopia, nystagmus, Chills, Hyponatraemia.

#### 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.

#### 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. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form [/https://sideeffects.health.gov.il](https://sideeffects.health.gov.il)

## 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 over dosage 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 naloxon 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 has to be strictly monitored (at least for 24 hours) since the duration of action of the opioid antagonist is shorter (naloxone 2-3 hours) 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  $\mu$ -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. Following epidural and intrathecal application locally limited analgesic effects are evident after a few minutes. The duration of action lasts about 12 hours following epidural use and is even longer in case of intrathecal administration. 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 fairly rapidly, 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-glucuronyltransferase 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 has to 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 as long as 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 off-spring during the entire duration of pregnancy (CNS malformation, growth retardation, testis 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 anhydrous, sodium edetate (dihydrate).

Total quantity of sodium is 0.17 mg/ml

### **6.2 Incompatibilities**

Not known.

### **6.3 Shelf life**

The expiry date of the product is indicated on the packaging materials

After opening of the bottle Oramorph® 20 mg/ml solution is stable for 90 days.

### **6.4 Special precautions for storage**

Do not store above 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 (N1).

### **6.6 Special precaution for disposal**

No special instructions.

## **7. MANUFACTURER**

L. Molteni & C. dei F.lli Alitti Società di Esercizio S.p.A.

Strada Statale 67, Frazione Granatieri

50018 Scandicci (Firenze)

Italy

## **8. LICENSE HOLDER AND IMPORTER**

BioAvenir Ltd.

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Herzeliya Pituach 4666101

**9. REGISTRATION NUMBER: 153-96-34100-00**

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