Patient leaflet in accordance with the Pharmacists' Regulations (Preparations) - 1986

This medicine is dispensed with a doctor's prescription only

Oramorph 20 mg/ml
Oral solution

Active ingredient
morphine (as sulfate)
Each ml (16 drops) contains 20 mg morphine (as sulfate)

Inactive ingredients and allergens in the medicine: see section 2 'Important information about some of this medicine's ingredients' and section 6 'Additional information'.
Read the entire leaflet carefully before you start using this medicine. This leaflet contains concise information about this medicine. If you have any further questions, consult your doctor or pharmacist.
This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if it seems to you that their medical condition is similar to yours.

Medicines of the opiate family may cause addiction, mainly upon prolonged use, and have a potential of misuse and overdose. The reaction to overdose can be manifested by slow breathing and may even cause death.
Make sure that you know the name of the medicine, the dose you take, administration frequency, treatment duration, side effects and potential risks.
Additional information about the risk of dependence and addiction is available in the following link:
https://www.health.gov.il/UnitsOffice/HD/MTI/Drugs/risk/DocLib/opioids_en.pdf

Taking this medicine with medicines of the benzodiazepine class, other medicines suppressing the central nervous system (including drugs) or alcohol may cause a sensation of deep drowsiness, difficulties in breathing (respiratory depression), coma and death.

1. What is this medicine intended for?

The medicine is intended for relief of moderate to severe pains

Therapeutic group: opioid painkillers.

2. Before using this medicine

Do not use this medicine if:

- You are sensitive (allergic) to the active ingredient morphine or to any of the other ingredients of this medicine (listed in section 6).
- You have bowel obstruction (ileus).
- You have unclear acute painful abdominal symptoms (acute abdomen).

Special warnings about using this medicine
Before taking Oramorph 20 mg/ml, tell your doctor if any of the following applies to you:

- Dependence on opioids
- Loss of consciousness
- Disease states in which a disturbance of the respiratory center and respiratory function is present
- Altered heart (cor pulmonale) due to chronic congestion of the pulmonary circulation
- Increased intracranial pressure
- Low blood pressure associated with low circulating blood volume (hypotension with hypovolemia)
- Enlarged prostate gland (prostatic hypertrophy) with residual urine (risk of bladder rupture (tear of the bladder) due to urinary retention)
- Urinary tract constrictions or colic
- Biliary diseases
- Obstructive (associated with stenosis) and inflammatory bowel disease
- Adrenal gland tumor (pheochromocytoma)
- Inflammation of the pancreas (pancreatitis)
- Underactive thyroid (hypothyroidism)
- Epileptic seizures or increased sensitivity to convulsions.

Talk to your doctor or pharmacist if you experience any of the following symptoms while taking Oramorph 20 mg/ml:

- Increased sensitivity to pain despite the fact that you are taking increasing doses (hyperalgesia). Your doctor will decide whether you will need a change in dose or a change in the strong analgesic type (see section 'Tolerance, dependence, and addiction').
- Weakness, fatigue, lack of appetite, nausea, vomiting or low blood pressure. These may be symptoms of the adrenals producing too little of the hormone cortisol, and you may need to take hormone supplement.
- Loss of libido, impotence, cessation of menstruation. This may occur because of decreased sex hormone production.
- If you have once been addicted to drugs or alcohol. Also, tell if you feel that you are becoming dependent on Oramorph 20 mg/ml while you are using it. You may have started to think a lot about when you can take the next dose, even if you do not need it for pain relief.
- Withdrawal symptoms or dependence. The most common withdrawal symptoms are listed in section 3. If this occurs, your doctor may change the type of medicine or the intervals between doses.

<u>Tolerance, dependence, and addiction</u>
This medicine contains morphine which is an opioid medicine. Repeated use of opioids can result in the drug being less effective (you become accustomed to it, known as tolerance). Repeated use of Oramorph 20 mg/ml can also lead to dependence, abuse, and addiction, which may result in life-threatening overdose. The risk of these side effects can increase with a higher dose and longer duration of use.

Dependence or addiction can make you feel that you are no longer in control of how much medicine you need to take or how often you need to take it.
The risk of becoming dependent or addicted varies from person to person. You may have a greater risk of becoming dependent on or addicted to Oramorph 20 mg/ml if:

- You or anyone in your family have ever abused or been dependent on alcohol, prescription medicines or illegal drugs ("addiction").
- You are a smoker.
- You have ever had problems with your mood (depression, anxiety, or a personality disorder) or have been treated by a psychiatrist for other mental illnesses.

If you notice any of the following signs whilst taking Oramorph 20 mg/ml, it could be a sign that you have become dependent or addicted:

- You need to take the medicine for longer than advised by your doctor
- You need to take more than the recommended dose
- You are using the medicine for reasons other than prescribed, for instance, 'to stay calm' or 'help you sleep'
- You have made repeated, unsuccessful attempts to quit or control the use of the medicine
- When you stop taking the medicine you feel unwell, and you feel better once taking the medicine again ('withdrawal effects')

If you notice any of these signs, speak to your doctor to discuss the best treatment pathway for you, including when it is appropriate to stop and how to stop safely (See section 3, 'If you stop taking the medicine').
In chronic pain patients, the risk of psychological dependence is significantly reduced or variable.

Acute generalized exanthematous pustulosis (AGEP) has been reported in association with Oramorph 20 mg/ml treatment. Symptoms usually occur within the first 10 days of treatment. Tell your doctor if you have ever developed a severe skin rash or skin peeling, blistering and/or mouth sores after taking Oramorph 20 mg/ml or other opioids. Stop using Oramorph 20 mg/ml and seek medical attention immediately, if you notice any of the following symptoms: blistering, widespread scaly skin or pus-filled spots associated with fever.

Sleep-related breathing disorders
Oramorph 20 mg/ml may cause sleep-related breathing disorders such as sleep apnea (breathing pauses during sleep) and sleep related hypoxemia (low oxygen level in the blood). The symptoms may include breathing pauses during sleep, night awakening due to shortness of breath, difficulties to maintain sleep or excessive drowsiness during the day. If you or another person observe these symptoms, contact your doctor. A dose reduction may be considered by your doctor.

Contact your doctor if you experience severe upper abdominal pain possibly radiating to the back, nausea, vomiting or fever as these could be symptoms associated with inflammation of the pancreas (pancreatitis) and the biliary tract system.

Oramorph 20 mg/ml should be administered with caution before and after surgery (increased risk of intestinal paralysis or respiratory depression).

What do you need to pay attention to?
Constipation is frequent during morphine treatment. You should take a laxative from the beginning of treatment, especially if you have had difficulties in bowel movements before you started taking the medicine. Please talk to your doctor if you experience this effect.

Elderly
In the elderly, Oramorph 20 mg/ml is to be dosed very carefully (see section 3).

Effects of misuse for doping
Use of Oramorph 20 mg/ml can lead to positive results in doping control tests.

Children and adolescents
Do not use this medicine in children under the age of 3 years.

Tests and follow-up
During prolonged treatment, you should undergo periodic assessments to evaluate further need of the medicine.

Drug interactions
If you are taking or have recently taken other medicines, including non-prescription medications and dietary supplements, tell your doctor or pharmacist.
Concomitant use of morphine with medicines acting on the central nervous system, i.e. on brain functions (such as medicines for treatment of anxiety disorders (tranquilizers), depression (antidepressants), mental disorders (antipsychotics), for anesthesia (anesthetics), medicines for treatment of insomnia (hypnotics, sedatives, barbiturates), allergy or travel sickness (antihistamines/antiemetics) or other potent painkillers (opioids)) or alcohol can lead to an increase in side effects of morphine, especially impairment of respiratory function.

Concomitant use of Oramorph 20 mg/ml with sedative medicines, such as benzodiazepines or related medicines, increases the risk of drowsiness, difficulties breathing (respiratory depression), coma and may be life-threatening. Because of this, concomitant use should only be considered when other treatment options are not possible. However if your doctor does prescribe Oramorph 20 mg/ml together with sedative medicines, the dose and duration of concomitant treatment should be limited by your doctor. Please tell your doctor about all the sedative medicines you are taking, and closely follow your doctor's recommendation regarding the dose. It could be helpful to inform friends or relatives to be aware of the signs and symptoms stated above. Contact your doctor if you experience such symptoms.

Medicines with anticholinergic activity (e.g. psychotropic drugs, medicines for allergies, vomiting or Parkinson's disease) may increase the anticholinergic side effects of opioids (e.g. constipation, dry mouth and urination disorders).

Cimetidine (used to treat stomach ulcers) and other medicines affecting liver metabolism may cause elevated levels of morphine in the blood by inhibiting morphine degradation.

Oramorph 20 mg/ml should not be administered concomitantly with MAO inhibitors (medicines against depression). After administration of MAO inhibitors within 14 days prior to the administration of another opioid (pethidine), life-threatening effects have been observed with respect to brain function (central nervous system), as well as respiratory and circulatory functions. The same interactions between MAO inhibitors and Oramorph 20 mg/ml as well cannot be excluded.

The effect of muscle relaxants may be enhanced by morphine.

Concomitant use with rifampicin (used to treat tuberculosis) may result in weakening of the effect of morphine.

The effect of some medicines used to treat blood clots (e.g. clopidogrel, prasugrel, ticagrelor) may be delayed and reduced if taken at the same time as morphine.

Gabapentin or pregabalin to treat epilepsy and pain due to nerve problems (neuropathic pain).

Using this medicine and food
The medicine can be taken independently of meal times.

Using this medicine and alcohol consumption
Do not drink alcohol during treatment with this medicine because alcohol may significantly increase the depressant effect of Oramorph 20 mg/ml.

Pregnancy, breastfeeding and fertility
Pregnancy
Studies in animals have demonstrated evidence of damages to the offspring of morphine treated mothers. Therefore, Oramorph 20 mg/ml should not be used in pregnancy, unless your doctor thinks that it is absolutely necessary and the benefits exceed the risk for the child.
If Oramorph 20 mg/ml is used for a long time during pregnancy, there is a risk of the newborn child having withdrawal symptoms, which should be treated by a doctor.
Breastfeeding
Morphine is excreted into breast milk and may reach effective concentrations in the infant. Breastfeeding is therefore not recommended.
Fertility
In view of the mutagenic properties of morphine, this medicine should be administered to men or women of reproductive age only when use of effective contraception is ensured.

Driving and using machines
Oramorph 20 mg/ml impairs attention and responsiveness. You cannot react quickly enough to unexpected and sudden events.
Discuss with your doctor whether and under what circumstances you can, for example, drive a car (see below). A stronger impact is to be expected especially at the beginning of treatment, with increase or change of dosage, as well as while taking the preparation in combination with alcohol or sedatives. Do not drive a car or other vehicles! Do not use electrical tools or machines! Do not work without a secure fit!

Important information about some of this medicine's ingredients
This medicine contains less than 1 mmol (23 mg) sodium per ml, that is to say essentially 'sodium-free'.
This medicine contains sodium benzoate at the concentration of 1 mg/ml.

3. How to use this medicine?

Always use this medicine according to your doctor's instructions. Check with your doctor or pharmacist if you are not sure about your dose or about how to take this medicine.

Before starting treatment and regularly during treatment, your doctor will discuss with you what you may expect from using Oramorph 20 mg/ml, when and how long you need to take it, when to contact your doctor, and when you need to stop it (see also 'If you stop taking the medicine' in this section).

Only your doctor will determine your dose and how you should take this medicine.
The recommended dosage is usually:
The dosage will be determined by your doctor depending on your age, weight, pain severity and response to treatment. Usually, a dose should be taken every 4 to 6 hours.
Do not exceed the recommended dose.
- Do not exceed 6 doses per day. If you continue experiencing pain during treatment with the medicine – contact your doctor.
- Do not change the dosage without your doctor's instruction.

Hepatic or renal dysfunction
In patients with impaired hepatic or renal function and suspected delayed gastrointestinal passage, Oramorph 20 mg/ml should be dosed very carefully.

Elderly
Patients in advanced age (usually 75 years of age and older) and patients with poor general physical condition may be more sensitive to morphine. Therefore, make sure that the dose adjustment is conservative and/or select longer dosing intervals. If necessary, switch to lower dosages.

Special instructions for dose adjustment
For readjustment of the dosage, possibly use forms with a lower content of active substance, also in addition to an existing therapy with prolonged-release tablets.

In principle, a sufficiently high dose should be given, while the smallest effective dose should be sought in the individual analgesic case. In case you undergo an additional pain treatment (e.g. surgery, plexus blockade (nerve block)), the dose will be reset. This will be done by your doctor in the specific case.

Method of administration
Take the medicine with a sufficient quantity of liquid - water or fruit juice. The medicine may be taken independently of meal times. Mix the drops with the liquid immediately before taking the medicine.
Each ml of the medicine contains 16 drops.
2 drops = 2.5 mg morphine sulfate
4 drops = 5 mg morphine sulfate
8 drops = 10 mg morphine sulfate
16 drops = 20 mg morphine sulfate
24 drops = 30 mg morphine sulfate

Treatment duration
The duration of the treatment will be determined by your doctor depending on the pain symptoms. In any case, Oramorph 20 mg/ml should be taken no longer than it is absolutely necessary.
If a long-term pain treatment with Oramorph 20 mg/ml appears to be necessary according to type and severity of the disease, careful and regular review should take place at short intervals (possibly with breaks in treatment, see section 'If you stop taking the medicine'), to determine whether and to what extent a medical need still exists. If necessary, switch to more appropriate forms.
In the treatment of chronic pain, a fixed dose schedule is to be preferred.

Please talk to your doctor or pharmacist if you have the impression that the effect of Oramorph 20 mg/ml is too strong or too weak.

If you have accidentally taken a higher dose, consult the nearest available doctor immediately.
If you have taken an overdose, or if a child or another person who is not the patient has accidentally swallowed some medicine, immediately go to a hospital emergency room and bring the medicine package with you.
The following symptoms may occur: small pupils, impaired breathing up to respiratory arrest, loss of consciousness up to coma, hypotension leading to shock, increase in heart rate, dizziness. Overdose of strong opioids may lead to a fatal outcome.
People who have taken an overdose may get pneumonia due to inhaling vomit or foreign matter; symptoms may include breathlessness, cough and fever.
Under no circumstances you are allowed to perform any activity that requires increased attention, such as driving a car.
The following measures are useful in case of overdose until the doctor arrives: keep awake, give orders to breath, provide breathing assistance.

If you have forgotten to take the medicine at the scheduled time, this leads to poor or lack of pain relief. Continue taking the medicine as recommended by your doctor. In any circumstances, do not take a double dose to compensate for the forgotten dose.

If you stop taking the medicine
If you want to interrupt or stop the treatment, you should talk to your doctor about the reasons for the interruption and other modes of treatment.
With prolonged use of Oramorph 20 mg/ml, a physical dependence can develop. Therefore, abrupt discontinuation of treatment will be accompanied by withdrawal symptoms. These can be body aches, headaches, muscle aches, tremors, fear, dissatisfaction, tension, restlessness, confusion, irritability, recurring insomnia, mood swings, hallucinations, seizures, diarrhea, abdominal pain, nausea, flu-like symptoms, rapid heartbeat and large pupils.
Since the risk of occurrence of withdrawal symptoms upon sudden discontinuation of treatment is high, the dosage should be reduced gradually when discontinuing the treatment.

Adhere to the treatment as recommended by your doctor.

Do not take medicines in the dark! Check the label and dose <u>every time</u> you take medicine. Wear glasses if you need them.

If you have any further questions about using this medicine, consult your doctor or pharmacist.

4. <u>Side effects</u>

Like with all medicines, using Oramorph 20 mg/ml may cause side effects in some users. Do not be alarmed by this list of side effects.
Stop the treatment and contact a doctor or a hospital emergency room immediately if the following side effects occur:

- Serious allergic reaction which causes difficulties breathing or dizziness.
- Severe skin reaction with blistering, widespread scaly skin, pus-filled spots associated with fever. This could be a condition called Acute Generalized Exanthematous Pustulosis (AGEP).

In the evaluation of side effects, the following frequencies are defined as:
Very common - affect more than 1 patient in 10
Common - affect less than 1 in 10 but more than 1 in 100 patients
Uncommon - affect less than 1 in 100 but more than 1 in 1,000 patients
Rare - affect less than 1 in 1,000 but more than 1 in 10,000
Very rare - affect less than 1 in 10,000 or unknown
Unknown frequency - The frequency of these effects has not been established yet

Additional side effects

<u>Immune system disorders</u>
Unknown frequency:
Acute general allergic reactions with drop in blood pressure and/or shortness of breath (anaphylactic reactions) can occur.

Disorders of the nervous system
Morphine leads to a dose dependent respiratory depression and sedation, varying from slight tiredness to dizziness.
Common: headache, dizziness.
Very rare: tremor, involuntary muscle twitching, epileptic seizures.
Particularly at high doses, increased sensitivity to pain that does not respond to further increase in the dose of morphine.

Psychiatric disorders
Morphine shows contrasting psychological side effects that occur individually and vary in intensity and nature (depending on the character and duration of treatment).
Very common: mood changes, excitement (euphoria), but also aggressiveness and general unhappiness (dysphoria).
Common: changes in awareness (usually reduction, but also increase or agitation), insomnia and disturbances in thinking and feelings (e.g. thought disorders, cognitive problems/hallucinations, confusion).
Very rare: dependence (see also section 2 'Special warnings about using this medicine'), decrease in libido or erectile dysfunction.

Eye disorders
Very rare: blurred vision, double vision and nystagmus.
Pupillary constriction is a typical side effect.

Disorders of the gastrointestinal tract
Dose related nausea and dry mouth may occur. With continuous treatment, constipation is a typical side effect.
Common: vomiting (especially at the beginning of treatment), loss of appetite, digestive and taste disorders.
Rare: increase of pancreatic enzymes or symptoms associated with inflammation of the pancreas (pancreatitis) and the biliary tract system, e.g. severe upper abdominal pain possibly radiating to the back, nausea, vomiting or fever.
Very rare: intestinal obstruction, abdominal pain.

Hepatobiliary disorders
Rare: biliary colic.
Very rare: increase in liver-specific enzymes.
Unknown frequency: spasm of the sphincter of Oddi.

Renal and urinary disorders
Common: problems in emptying the bladder.
Rare: renal colic.

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

Respiratory disorders
Rare: spasms of the airway muscles (bronchospasm).
Very rare: shortness of breath (dyspnea).
Unknown frequency: sleep apnea (breathing pauses during sleep).

In intensive care patients, fluid retention in the lungs that is not due to failure of cardiac function (non-cardiogenic pulmonary edema) has been observed.

Skin and subcutaneous tissue
Common: sweating, hypersensitivity reactions such as urticaria (hives), itching (pruritus).
Very rare: skin rash and fluid accumulation in the tissues (peripheral edema) - these effects resolve after treatment discontinuation.

Heart disorders
Uncommon: clinically significant drop and rise in blood pressure and heart rate. Facial flushing, palpitations, general weakness up to fainting and heart failure may occur.

General disorders
The treatment may cause habituation, and eventually decrease in the activity (development of tolerance).
Rare: withdrawal symptoms.
Very rare: asthenia (weakness), malaise, chills, absence of menstruation.

Endocrine disorders
Very rare: A syndrome of inappropriate release of antidiuretic hormone (SIADH; symptom: lack of sodium (hyponatremia) may develop).

Countermeasures
If you observe signs of the aforementioned serious side effects, call the nearest doctor for help.
In case of other side effects, please talk with your doctor about another treatment.

If you experience any side effect, if any side effect gets worse, or if you experience a side effect not mentioned in this leaflet, consult your doctor.

You can report side effects to the Ministry of Health by following the link 'Reporting Side Effects of Drug Treatment' on the Ministry of Health home page (www.health.gov.il) which links to an online form for reporting side effects. You can also use this link: https://sideeffects.health.gov.il

5. How to store the medicine?

- Prevent poisoning! To prevent poisoning, keep this and all other medicines in a closed place, out of the reach and sight of children and/or infants. Do not induce vomiting unless explicitly instructed to do so by a doctor.
- Do not use the medicine after the expiry date (exp. date) which is stated on the carton package and label. The expiry date refers to the last day of that month.
- Oramorph 20 mg/ml can be used for 90 days after opening the package.
- Storage conditions:
  Store below 25°C.
  Store in the original package to protect from light.

6. Additional information

- **In addition to the active ingredient, this medicine also contains:**
  Purified water, citric acid anhydrous, sodium benzoate, disodium edetate (dihydrate).

- **What the medicine looks like and contents of the pack:**
  A clear and colorless solution in a brown glass bottle containing 20 ml, with a calibrated dropper enclosed.

- **Registration holder's and importer's name and address:** BioAvenir Ltd., 1 David Hamelech St., Herzeliya Pituach 4666101.

- **Manufacturer's name and address:** L. Molteni & C. Ltd., Scandicci (Florence), Italy.
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  Strada Statale 67, Tosco Romagnola, 50018- Fraz. Granatieri-Scandicci (Firenze) Italy

- Revised in January 2024.

- Registration number of the medicine in the National Drug Registry of the Ministry of Health: 153-96-34100-00.