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 sulfate
Each ml (16 drops) contains 20 mg morphine sulfate

Inactive ingredients and allergens: see section 2 "Important information about some of this medicine's ingredients" and section 6 "Additional information".
For detailed information regarding the method of administration, see section 3.

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. This is especially important while using this type of medicine, which has been prescribed to you after careful evaluation of the benefit against the risk of its unnecessary use.
The medicine is not intended for children below the age of 3 years.

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

1. What is this medicine intended for?

The medicine is intended for relief of moderate to severe pains not responding to non-opioid painkillers.

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 breathing probelms, such as respiratory depression or diseases obstructing the airways.

- You have bowel obstruction (ileus), severe abdominal pain or slow gastric emptying.
- You have an acute liver disease.
- You suffer from head injury.
- You are severely addicted to alcohol.
- You are currently taking, or have taken during the last 2 weeks, a medicine of the MAO inhibitors family (MAOIs).
- You are pregnant or breastfeeding.
- Do not use this medicine in children below the age of 3 years.
- The patient is in a state of persistent lack of consciousness or coma.
- You have increased intracranial pressure or convulsions.
- You have a pheochromocytoma (a benign adrenal gland tumor)

Special warnings about using this medicine

- Oramorph 20 mg/ml contains morphine, an opioid component, which has a potential of misuse. Take all the precautions to keep the medicine out of the reach of a person who is not the patient.
- Prolonged use may cause dependence!
- Keep the medicine in a safe place out of the reach of children. Unintentional ingestion of the medicine, especially by children, may cause a life-threatening damage.
- Do not stop taking this medicine suddenly without consulting a doctor! Treatment discontinuation will be done according to your doctor's instructions (gradually) to avoid occurrence of withdrawal symptoms, such as restlessness, anxiety, tremor and sweating.
- Avoid sudden transition from lying/sitting position to standing position to avoid dizziness, and in extreme cases fainting.
- If you are about to undergo surgery (including dental) or any other procedure involving anesthesia, inform the doctor about taking this medicine. Use is not recommended prior to surgery up to 24 hours after surgery, unless instructed to do so by the doctor.
- Great caution is required in the elderly due to their increased sensitivity to the medicine.
- If you are sensitive to any food or medicine (especially to other opioid painkillers), inform your doctor before taking the medicine.

Before taking Oramorph 20 mg/ml, tell your doctor or pharmacist if:

- You are trying to become pregnant.
- You have impaired respiratory function, disturbance of the respiratory center (such as bronchial asthma or impaired pulmonary function).
- You have impaired cardiovascular function (e.g. low blood pressure or right heart failure known as cor pulmonale). A heart disease due to chronic congestion of the pulmonary circulation.
- You have adrenal gland disease, such as Addison's disease, pheochromocytoma.
- You have impaired liver function.
- You have impaired kidney/urinary system function (including urinary tract constriction/colic).

- You have impaired gallbladder function.
- You have impaired gastrointestinal function (such as obstructive (associated with stenosis) and inflammatory bowel disease).
- You have an enlarged prostate gland (prostatic hypertrophy) with residual urine (at risk of bladder rupture due to urinary retention).
- You have or have had Inflammation of the pancreas (pancreatitis).
- You have or have had underactive thyroid (hypothyroidism).
- You have or have had epilepsy or convulsions, or increased predisposition to convulsions.
- You are or have been addicted to alcohol, drugs or medicines **(there is opioid dependence).**
- Low blood pressure associated with low blood volume (hypotension with hypovolemia).
- You have had withdrawal symptoms following discontinuation of medicines or drugs, such as restlessness, anxiety, tremor or sweating.
- You have kyphoscoliosis.
- You are obese.

Talk to your doctor or pharmacist if you experience any of the following symptoms while taking Oramorph 20 mg/ml solution:
- 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 2).
- 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 been addicted to drugs or alcohol. Also, tell if you feel that you are becoming dependent on Oramorph 20 mg/ml solution 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.

In chronic pain patients, the risk of psychological dependence is significantly reduced or variable.

Oramorph 20 mg/ml solution 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.

Men and women of reproductive age
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.

Children
Do not use this medicine in children below the age of 3 years.

Older population
In older people, Oramorph 20 mg/ml solution is to be dosed very carefully (see section 3).

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

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. Particularly if you are taking the following medicines (of note, the following list indicates the active ingredients in the medicines. If you are not sure whether you are using any of these medicines, please consult 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), medicines for treatment of certain mental disorders and depression (such as phenothiazines, neuroleptics and antidepressants), medicines for treatment of insomnia (hypnotics, sedatives, barbiturates), medicines for treatment of allergy or travel sickness (antihistamines/antiemetics), anesthetics for surgeries and other painkillers (opioids)) or alcohol may lead to an increase in side effects of morphine, especially impairment of respiratory function.
- Medicines for treatment of high blood pressure.
- Gabapentin (for treatment of epilepsy or neuropathic pain).
- Ritonavir (for treatment against the HIV/AIDS virus).
- Mexiletine and esmolol for arrhythmias.
- Voriconazole for treatment of fungal infections.
- Buprenorphine, nalbuphine and pentazocine – painkillers.

Concomitant use of Oramorph 20 mg/ml solution 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 solution 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 and vomiting, such as domperidone or metoclopramide, 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 solution should not be administered concomitantly with MAO inhibitors (medicines that are effective against depression). See section 2 "Do not use this medicine if". 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 solution 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 with morphine.

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

Using this medicine and alcohol consumption
Do not drink alcohol during treatment with this medicine.
Drinking alcohol while using this medicine may make you feel sleepy, since alcohol may significantly increase the depressant effect of Oramorph 20 mg/ml solution.

Pregnancy and breastfeeding
Do not use this medicine if you are pregnant or breastfeeding.
Pregnancy
Studies in animals have demonstrated evidence of damages to the offspring of morphine treated mothers. Therefore, Oramorph 20 mg/ml solution should not be used in pregnancy, unless your treating physician thinks that it is absolutely

necessary and the benefits exceed the risk to the fetus. In view of the mutagenic properties of morphine, men and women of reproductive age should take it only if use of effective contraception is ensured.
If Oramorph 20 mg/ml solution is used for a long time during pregnancy, there is a risk of the newborn child having withdrawal symptoms, which must 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.

Driving and using machines
Use of this medicine may impair alertness, thus requiring caution while driving a vehicle, operating dangerous machines and performing any activity requiring alertness. Children should be warned against riding a bicycle or playing near the road, etc.
Oramorph 20 mg/ml solution 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 as a preservative at the concentration of 1 mg/ml. Sodium benzoate may make jaundice (yellowing of the skin and eyes) worse in newborn babies (up to 4 weeks of age).

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.

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 solution should be dosed very carefully.

Elderly
Patients in advanced age (usually 75 years of age) 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 dosage strengths.

Special instructions for dose adjustment
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.

Take the medicine with a sufficient quantity of liquid - water or fruit juice. Drink the entire quantity to ensure intake of the required dose. The medicine may be taken independently of the eating 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 solution should be taken no longer than it is absolutely necessary.
If a long-term pain treatment with Oramorph 20 mg/ml solution 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 preparations.
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 solution 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**.**

Symptoms of overdose may include nausea, dizziness, severe drowsiness. In severe cases, breathing difficulties may occur, which may cause loss of consciousness and even death. These symptoms require urgent medical assistance.
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, take a dose as soon as you remember, but in any case, there should be an interval of no less than 4 hours between one dose to another. Never take a double dose to compensate for the forgotten dose.

If you stop taking the medicine
Do not stop taking the medicine suddenly, unless your doctor has instructed you to do so.
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 solution, a physical dependence may develop. Therefore, abrupt discontinuation of treatment will be accompanied by withdrawal symptoms. These may 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 higher, the dosage should be reduced gradually when discontinuing the treatment.

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

If you want to stop taking the medicine, consult your doctor, who will guide you how to do it without experiencing withdrawal symptoms, such as restlessness, anxiety, tremor or sweating.

How can you assist in treatment success?
Adhere to the treatment as recommended by your doctor.
Even if your health improves, do not stop taking this medicine without consulting your doctor, and even then, you should do it gradually.

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

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

4. Side effects

Like with all medicines, using Oramorph may cause side effects in some users. Do not be alarmed by this list of side effects; you may not experience any of them. However, if the side effects are persistent or bothering, or worsen, consult your doctor.

In the evaluation of side effects, the following frequencies are defined as:
Very common: frequency of more than 1 in 10 patients.
Common: less than 1 in 10 but more than 1 in 100 patients.
Uncommon: less than 1 in 100 but more than 1 in 1,000 patients.
Rare: less than 1 in 1,000 but more than 1 in 10,000.
Very rare: less than 1 in 10,000 or unknown.
Unknown frequency: frequency cannot be estimated from the available data.

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.
- Allergic or anaphylactic reaction (also manifested by swelling in the facial area, eyelids or lips, rash and itching in extensive areas), respiratory depression, slow and weak breathing, convulsions, deep drowsiness, excessive sweating, severe abdominal pain, intestinal obstruction, loss of consciousness.

Possible side effects:

Immune system disorders
Unknown frequency:
Acute general allergic reactions with drop in blood pressure and/or shortness of breath (anaphylactic reactions) may 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 "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: elevation of pancreatic enzymes or inflammation of the pancreas (pancreatitis).
Very rare: intestinal obstruction, abdominal pain.

Hepatobiliary disorders
Rare: biliary colic.
Very rare: increase in liver-specific enzymes.

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).
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.

Rarely occurring side effects (in 1:100 to 1:1,000 patients)
Numbness or tingling, difficulty urinating, facial redness (flushing), swelling of the hands, ankles or legs, urticaria (hives), blurred vision, muscle cramps.

Rare side effects
Double vision, nystagmus

Side effects of unknown frequency
Depressed mood, unusual thoughts, rapid or slow heart beats, constricted pupils, high blood pressure, decreased cough reflex, abdominal cramps, worsening of pancreatitis symptoms, absence of menstruation, impotence, reduced libido, vision disturbances, pupil constriction and tolerance to the medicine.

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.

Side effects and drug interactions in children
Parents must inform the treating doctor on any side effect and any additional medicine given to the child. See side effects and drug interactions above.

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, which may cause a life-threatening damage, keep this and all other medicines in a closed place, out of the reach and sight of children and/or infants. See sections "Special warnings about using this medicine" and "If you have accidentally taken a higher dose".
- 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 solution is stable 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, sodium edetate (dihydrate).

- What the medicine looks like and contents of the pack:
  A clear and colorless solution in a brown 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.

- This leaflet was revised in December 2021 according to MOH guidelines.

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