Package leaflet: Information for the user

Methadone hydrochloride 1 mg/ml oral solution
Methadone hydrochloride

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Methadone hydrochloride is and what it is used for

This medicine contains methadone hydrochloride, which belongs to a group of medicines called narcotic analgesics. It is used as part of the treatment of opioid addiction.

All patients receiving Methadone hydrochloride must be routinely monitored for signs of misuse, abuse, and addiction during treatment.

2. What you need to know before you take Methadone hydrochloride

Do not take Methadone hydrochloride if:
- you are allergic to methadone or any of the other ingredients of this medicine (listed in section 6). An allergic reaction includes a rash, itching or shortness of breath;
- you are having an asthma attack. You should not use this medicine during an asthma attack. If you give this medicine to yourself (self-administration), wait until the asthma attack has passed and you are fully recovered;
- your breathing is very slow or shallow (respiratory depression);
- you are addicted to alcohol;
- you have suffered a recent head injury or have an increased pressure in the brain;
- you are taking monoamine oxidase inhibitors (MAOIs) used to treat depression or if you have taken MAOI medicine in the past two weeks (See "Other medicines and Methadone hydrochloride");
- you are not dependent on opioid substances;
- you have heart problems (QT prolongation);
- you have severe liver problems;

- you are suffering from a bowel condition called ulcerative colitis;
- you have spasm of the urinary tract (causing pain in the lower back and urination problems);
- you have spasm of the biliary tract (causing pain under the right ribcage, usually after a meal);
- you are in labour.

If you are not sure if any of the above applies to you, talk to your doctor or pharmacist before taking Methadone hydrochloride.

Warnings and precautions
Talk to your doctor or pharmacist before taking Methadone hydrochloride if you:
- have severe breathing problems;
- have or have recently had a head injury;
- have liver or kidney problems;
- have epilepsy;
- have an underactive pituitary gland (hypopituitarism);
- have low thyroid function (hypothyroid);
- have underactive adrenal glands;
- have a tumor of the adrenal glands (phaeochromocytoma);
- have an enlarged prostate gland;
- have low blood pressure;
- are in shock (circulatory failure);
- have a muscle weakness disease called myasthenia gravis;
- have bowel problems;
- have recognized risk factors for QT prolongation that include if you:
    - have a history of irregular heart beat;
    - have a history of heart disease;
    - have a family history of people dying suddenly without cause;
    - have low potassium, sodium or magnesium levels;
- are pregnant or breast-feeding;
- are extremely ill or an older person. You may be more sensitive to the medicine.

Talk to your doctor or pharmacist if you experience any of the following symptoms while taking Methadone hydrochloride: weakness, fatigue, lack of appetite, nausea, vomiting or low blood pressure. This may be a symptom of the adrenals producing too little of the hormone cortisol, and you may need to take hormone supplement (see section 4).

Long-term use may cause decreased sex hormone levels and increased levels of the hormone prolactin. Contact your doctor if you experience symptoms such as decreased libido, impotence, absence of menstruation (amenorrhea) or infertility.

Sleep-related breathing disorders
Methadone hydrochloride can cause sleep-related breathing disorders such as sleep apnoea (breathing pauses during sleep) and sleep related hypoxemia (low oxygen level in the blood). The symptoms can 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.

Tolerance, dependence, and addiction
This medicine contains methadone 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 Methadone hydrochloride can also lead to dependence, abuse, and addiction, which may result in life-threatening overdose.

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 or addicted on Methadone hydrochloride 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 Methadone hydrochloride, 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 Methadone hydrochloride).

If you are not sure if any of the above applies to you, talk to your doctor or pharmacist before taking Methadone hydrochloride.

Other medicines and Methadone hydrochloride
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

Methadone hydrochloride can affect the way some other medicines work. Also some medicines can affect the way it works.
You must not take Methadone hydrochloride:
- at the same time or within 2 weeks of taking monoamine oxidase inhibitors (MAOIs)

In particular, tell your doctor if you are taking any of the following medicines:
- other opiate analgesics;

- medicines that have effect on your mental state (e.g. thioridazine, phenothiazines, haloperidol and sertindole);
- medicines for heart problems such as verapamil and quinidine;
- medicine to treat depression (desipramine, nefazodone, fluvoxamine, fluoxetine, paroxetine and sertraline);
- anti-inflammatory and immunosuppressants (e.g. dexamethasone and ciclosporin);
- antiviral medications including some medicine used to treat HIV (nevirapine, zidovudine, efavirenz, nelfinavir, ritonavir, amprenavir, delavirdine, lopinavir/ritonavir, ritonavir/saquinavir, abacavir, didanosine and stavudine);
- antibiotics (medicines used to treat bacterial infections) such as ciprofloxacin and macrolide antibiotics for example clarithromycin, telithromycin and erythromycin;
- medicines used to treat fungal infections such as fluconazole, itraconazole and ketoconazole;
- cimetidine, used to treat stomach ulcers;
- naloxone used to reverse the effect of opioids;
- medicines used to stop opioids working such as naltrexone and buprenorphine;
- rifampicin, used to treat tuberculosis (TB);
- medicines used to treat epilepsy such as phenytoin, carbamazepine, phenobarbital and primidone;
- cannabidiol (a medicine used to treat seizures);
- gabapentin and pregabalin (medicines used to treat epilepsy, nerve pain or anxiety), can increase the risk of opioid overdose, respiratory depression (breathing difficulties) and may be life-threatening;
- medicines that make your urine acidic, such as ascorbic acid (vitamin C) and ammonium chloride;
- medicine used to treat diarrhoea (e.g. loperamide, diphenoxylate);
- diuretic medicine (e.g. spironolactone);
- medicine that makes you feel sleepy;
- metamizole, a medicine used to treat pain and fever;
- St. John's Wort – a herbal preparation for depression.

The risk of side effects increases, if you use methadone concomitantly with antidepressants (such as citalopram, duloxetine, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline, venlafaxine, amitriptyline, clomipramine, imipramine, nortriptyline). Contact your doctor if you experience symptoms such as:

- mental-status changes (e.g. agitation, hallucinations, coma)
- fast heartbeat, unstable blood pressure, fever
- exaggeration of reflexes, impaired coordination, muscle stiffness
- gastrointestinal symptoms (e.g. nausea, vomiting, diarrhoea) (see section 4).

Concomitant use of Methadone hydrochloride and sedative medicines such as benzodiazepines or related drugs increases the risk of drowsiness, difficulties in 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 Methadone hydrochloride together with sedative medicines the dose and duration of concomitant treatment should be limited by your doctor.
Please tell your doctor about all sedative medicines you are taking, and follow your doctor’s dose recommendation closely. It could be helpful to inform friends or relatives to be aware of the signs and symptoms stated above. Contact your doctor when experiencing such symptoms.

Other medicines you may be taking can also affect the heart (e.g sotalol, amiodarone and flecainide). You must tell your doctor about any other medicine that you are taking as they may be dangerous if they are taken with methadone. In these situations your doctor may decide that it is necessary to monitor your heart with an electrocardiogram (ECG) at the start of treatment to ensure that these effects do not occur.

Methadone may also affect some blood and urine tests (including doping tests). Please tell your doctor if you are taking methadone before any test is performed.

Methadone hydrochloride with food, drink and alcohol
Methadone hydrochloride can be taken with or without food.
Do not drink alcohol whilst taking Methadone hydrochloride. This is because methadone can make you feel sleepy and drinking alcohol will make you even sleepier.
Do not drink grapefruit juice whilst taking Methadone hydrochloride. This is because grapefruit juice may alter the effect of methadone.

Pregnancy, breast-feeding and fertility
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before taking this medicine.
Take care if you are taking a pregnancy test as Methadone hydrochloride may interfere with the results.
You should not take this medicine whilst you are in labour.
Talk to your doctor if you are breastfeeding or thinking of breast-feeding while you are taking methadone as it may affect your baby. Monitor your baby for abnormal signs and symptoms such as increased drowsiness (more than usual), breathing difficulties or limpness. Consult your doctor immediately if you notice any of these symptoms.

Driving and using machines
Methadone may severely affect your ability to drive or use machines, whilst taking it and afterwards. You should only start doing these activities again with the permission of your doctor.

Methadone hydrochloride contains sorbitol.
This medicine contains 21 mg sorbitol in each 1 ml.
Sorbitol is a source of fructose. If your doctor has told you that you have an intolerance to some sugars or if you have been diagnosed with hereditary fructose intolerance (HFI), a rare genetic disorder in which a person cannot break down fructose, talk to your doctor before you take or receive this medicine.

In some individuals sorbitol can affect how much methadone is absorbed from the swallowed dose. In these individuals, switching between Methadone hydrochloride 1 mg/ml oral solution and other methadone products, which do not contain sorbitol, can cause change in methadone blood levels and return of symptoms. If this happens, please contact your doctor.

Methadone hydrochloride contains sodium benzoate.
This medicine contains 3 mg sodium benzoate in each 1 ml.

Methadone hydrochloride contains color sunset yellow.
It may cause allergic reactions.

Methadone hydrochloride contains sodium.
This medicine contains 0.478 mg sodium (main component of cooking/table salt) in each 1 ml. When the maximum daily dose (150 mg) of methadone is taken, the quantity of sodium would be equivalent to approximately 3.59 % of the recommended maximum daily dietary intake of sodium for an adult.

3. How to take Methadone hydrochloride

Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

You must only take Methadone hydrochloride by mouth. Under no circumstances should you inject this product as injection as it may cause serious and permanent damage to your body with the possibility of fatal consequences.
Your doctor will tell you how much Methadone hydrochloride you need to take, and how often you need to take it. It is important that you do not take more than the dose agreed with your doctor.

Adults
The usual starting dose is 10-30 mg a day. The dose will be slowly increased until you show no signs of withdrawal or intoxication. The usual dose is 60-120 mg/day. Your doctor will decide what dose you need and when to reduce the dose.

Older people
The doctor may reduce your dose and monitor you more closely.

Patients with kidney or liver disease
The doctor may reduce your dose and monitor you carefully. If you suffer from severe liver problems you should not be given this medicine.

Use in children and adolescents
Methadone hydrochloride is not suitable for children and adolescents.

If you take more Methadone hydrochloride than you should
If you take too much methadone you can experience the following:
- difficulty breathing, slow or shallow breathing;
- extreme sleepiness, fainting or coma;
- pinpoint pupils;
- muscle weakness;
- cold and clammy skin;
- low blood sugar;
- slow heartbeat, low blood pressure, shock (circulatory failure), cardiac arrest;
- a brain disorder (known as toxic leukoencephalopathy);
- in severe cases death may occur.

In the event of overdose you should seek medical assistance immediately even if you feel well as you may be suffering from methadone poisoning.

If you forget to take Methadone hydrochloride
If you forget a dose do not take it. Wait until the next dose is due and take only that amount. Do not take a double dose to make up for a forgotten dose.

If you stop taking Methadone hydrochloride
Do not stop taking this medicine unless your doctor tells you to as you may suffer withdrawal effects (see section 4). Your doctor will tell you how to lower the dose gradually.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can have undesirable effects, although not everybody gets them.

Stop taking this medicine and see a doctor straight away if you have any of the following:
- allergic reaction which may include: swelling of your face, lips, tongue or throat or difficulty breathing or swallowing or severe itching of your skin with raised lumps;
- serious heart problems; the signs of this may include changes in the way your heart beats, such as it beating faster or missed heart beats, breathing difficulties and dizziness, cardiac arrest;
- if your breathing becomes slow and shallow;

- worsening of the pressure inside your head if you already have this condition following an injury to your brain or brain disease.

Keep taking the medicine but tell your doctor straight away if you get any of the following side effects:
- if you have asthma and it gets worse.

Other possible side effects include:

Very common (may affect more than 1 in 10 people):
- feeling or being sick.

Common (may affect up to 1 in 10 people):
- water/fluid retention;
- feeling high (euphoria), seeing or hearing things that are not real (hallucinations), confusion;
- feeling sleepy (sedation);
- blurred vision, pin point pupils, dry eyes;
- feeling of dizziness or spinning;
- constipation;
- transient rash, sweating;
- feeling tired; drowsiness;
- weight increase.

Uncommon (**may affect up to 1 in 100 people):**
- feeling down (dysphoria), agitation, difficulty sleeping, disorientation, reduction of sex drive;
- headache, fainting;
- low blood pressure, facial flush;
- breathing difficulty (including with cough) due to accumulation of fluid in the lungs, worsening of asthma, dry nose;
- dry mouth, inflammation of the tongue;
- bile duct spasm (abdominal pain);
- itching, hives, rash, bleeding hives;
- urine retention (difficulty in passing urine), decreased urine production;
- reduced potency, disturbances of menstruation, production of breast milk;
- swelling of the legs; swelling (oedema);
- weakness;
- low body temperature.

Rare (may affect up to 1 to 1,000 people):
- slower heart beat, feeling your heart beat (palpitations);
- collapse, shock;
- respiratory arrest;
- intestinal hypomotility (ileus).

The following side effects have also been reported (frequency not known):
- lower levels of platelets in blood (in opioid-dependent patients with chronic hepatitis), which increases the risk of bleeding or bruising;
- increased prolactin levels;
- underactive adrenal gland (with symptoms such as: nausea or vomiting, loss of appetite, fatigue, weakness, dizziness, low blood pressure);

- loss of appetite;
- blood potassium or magnesium deficiency;
- low blood sugar;
- serotonin syndrome (see section 2);
- nystagmus (involuntary eye movement);
- hearing loss;
- spasm of the urinary tract (causing pain in the lower back and urination problems);
- prolonged use of methadone is associated with breast enlargement in men, impaired fertility, sexual dysfunction, decreased sex hormones;
- you can become dependent on Methadone hydrochloride for more information see section 2 Warnings and Precautions);
- sleep apnoea (breathing pauses during sleep).

Withdrawal symptoms may be observed after discontinuation of treatment and include: body aches, diarrhoea, erection of the hair on the skin, loss of appetite, nervousness or restlessness, sneezing, runny nose, tremors or shivering, abdominal cramps, nausea, sleep disturbance, increase in sweating and yawning, weakness and unexplained fever. Some people may notice that their heart is beating a little faster or more forcefully. With appropriate dose adjustments and gradual withdrawal these symptoms are usually mild.

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects via:
HPRA Pharmacovigilance
Website: www.hpra.ie.
By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Methadone hydrochloride

Keep this medicine out of the sight and reach of children. Store this medicine in a safe and secure storage space, where other people cannot access it. It can cause serious harm and be fatal to people when it has not been prescribed for them.
Do not use this medicine after the expiry date which is stated on the carton and bottle after EXP. The expiry date refers to the last day of that month.
Store in the original package in order to protect from light.
After first opening, this medicine should be used within 90 days, when stored in the original package in order to protect from light.
This medicinal product does not require any special temperature storage conditions.
Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines no longer required. These measures will help to protect the environment.

6. Contents of the pack and other information

What Methadone hydrochloride contains
- The active substance is methadone hydrochloride.

Each 1 ml of the oral solution contains 1 mg of methadone hydrochloride.
- The other ingredients are: sorbitol, liquid non-crystallising (E420); glycerol (E422); sodium benzoate (E211); citric acid monohydrate (E330), colour brilliant blue FCF (E133), colour sunset yellow FCF (E110) and water, purified.

What Methadone hydrochloride looks like and contents of the pack
Methadone hydrochloride is a clear green solution.
<u>100 ml pack size:</u>

Carton box with a glass bottle containing 100 ml oral solution with child-resistant plastic cap and a leaflet inside.
1000 ml pack size:
Carton box with a bottle containing 1000 ml oral solution with child-resistant plastic cap and a leaflet inside.

Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer
Alkaloid-INT d.o.o.
Šlandrova ulica 4
1231 Ljubljana-Črnuče, Slovenia
email: info@alkaloid.si

This medicine is authorised in the Member States of the European Economic Area and in the United Kingdom (Northern Ireland) under the following names:

Ireland	Methadone hydrochloride 1 mg/ml oral
Croatia	Metadon Alkaloid 1 mg/ml oralna otopina
Malta	Methadone Alkaloid 1 mg/ml oral solution
Poland	Methadone hydrochloride INN-FARM
United Kingdom (Northern Ireland)	Methadone Alkaloid 1 mg/ml oral solution

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