PATIENT INFORMATION LEAFLET

SCHEDULING STATUS: S6

MISYO 10 mg/ml oral solution

Methadone hydrochloride

Sugar free

Each 1 ml of the oral solution contains 300 mg of sorbitol, liquid non-crystallising (E420) (which is equivalent to 210 mg of sorbitol).

Each 1 ml of the oral solution contains 3 mg sodium benzoate (E211) as preservative.

Each 1 ml of the oral solution contains 0,478 mg (0,021 mmol) sodium.

Read all of this leaflet carefully before you take MISYO

- Keep this leaflet. You may need to read it again.
- If you have any further questions, please ask your doctor, pharmacist, nurse or other health care provider.
- MISYO has been prescribed for you personally and you should not share your medicine with other people. It may harm them, even if their symptoms are the same as yours.

What is in this leaflet

1. What MISYO is and what it is used for.
2. What you need to know before you take MISYO
3. How to take MISYO
4. Possible side effects
5. How to store MISYO

6. Contents of the pack and other information

1. What MISYO 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 in the treatment of opiate/opioid addiction in order to reduce withdrawal symptoms.

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

2. What you need to know before you take MISYO

Do not take MISYO:

- if you are allergic (hypersensitive) to methadone, benzoates or to any of the other ingredients (listed in section 6).
- if you are having an asthma attack. You should not use MISYO during an asthma attack. If you give MISYO to yourself (self-administration), wait until the asthma attack has passed and you are fully recovered.
- if you are addicted to alcohol.
- if you are taking monoamine oxidase inhibitors (MAOIs) used to treat depression or if you have taken MAOI medicine in the past two weeks (See "Taking other medicines").
- if you have lower consciousness (feeling less alert or aware than normal).
- if you have a head injury.
- if you have heart problems relating to the way in which it conducts electricity (QT prolongation).
- if you have severe liver problems.
- if you have difficulty breathing (respiratory depression).

- in children.

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

Warnings and precautions

Talk to your doctor or pharmacist before taking MISYO. Take special care with MISYO if you:

- have breathing problems or asthma.
- have recently had a head injury.
- have liver or kidney problems.
- have epilepsy.
- have low thyroid function (hypothyroid).
- have problems with your adrenal glands (glands which produce hormones).
- have an enlarged prostate gland.
- have low blood pressure.
- are in shock.
- have a muscle weakness disease called myasthenia gravis.
- have bowel problems.
- have diabetes or difficulty to regulate your blood sugar.
- have recognized risk factors for QT prolongation (a condition affecting the ability of your heart to conduct electricity) they are:
  - have a history of irregular heartbeat.
  - have a history of heart disease.
  - have a family history of people dying suddenly without cause.
  - have low potassium, sodium or magnesium levels in your blood.

- have been using MISYO for a long time, as it may become less effective over time and you could develop tolerance and dependence. The risks of developing dependence are increased if you have a current or past history of substance misuse disorders, e.g. alcohol use disorder, opioid (strong pain medication, e.g. morphine) use disorder or drug use disorder.
- are extremely ill or an older person. You may be more sensitive to MISYO and may need your dose adjusted.

If during treatment you notice that your breathing becomes slow and shallow, stop taking MISYO and see a doctor straight away. These may be signs of respiratory depression (see section 4) and may not be fully apparent for a week or two.

You and your caregiver must be aware of the signs of excessive dosing, as addressed below in section 3, subsection “If you take more MISYO than you should”.

Talk to your doctor or pharmacist if you experience any of the following symptoms while taking MISYO: weakness, fatigue, lack of appetite, nausea, vomiting or low blood pressure. This may be a symptom of your adrenal glands producing too little of the hormone cortisol, and you may need to take a hormone supplement.

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 or absence of menstruation (amenorrhea).

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

Children

MISYO must not be administered to children, as it can cause breathing difficulties.

Other medicines and MISYO

Always tell your healthcare professional if you are taking any other medicine (this includes complementary or traditional medicines).

MISYO can affect the way some other medicines work. Also some medicines can affect the way that it works.

You must not take MISYO:

- at the same time or within 2 weeks of taking monoamine oxidase inhibitors (MAOIs - used to treat depression) (e.g. selegiline).

In particular, tell your doctor if you are taking any of the following medicines:

- other opiate/opioid analgesics (strong pain medicine, e.g. morphine, pethidine).
- medicines that have effect on your mental state (e.g. thioridazine, phenothiazines, haloperidol and sertindole).
- medicines for heart problems (e.g. sotalol, amiodarone, flecainide, verapamil, quinidine).
- medicines used to treat depression (e.g. desipramine, nefazodone, fluvoxamine, fluoxetine, paroxetine and sertraline).
- chloral hydrate (used to treat sleeplessness (insomnia)).
- chlormethiazole (used for the treatment of alcohol withdrawal).
- anti-inflammatory and immunosuppressant's (e.g. dexamethasone and ciclosporin).

- antiviral medicines, including some medicine used to treat HIV (e.g. nevirapine, zidovudine, efavirenz, nelfinavir, ritonavir, amprenavir, delavirdine, lopinavir/ritonavir, ritonavir/saquinavir, abacavir, didanosine, stavudine).
- antibiotics (medicines used to treat bacterial infections, e.g. ciprofloxacin and macrolilide antibiotics for example clarithromycin, telithromycin, erythromycin).
- medicines used to treat fungal infections (e.g. fluconazole, itraconazole, ketoconazole).
- cimetidine (used to treat stomach ulcers).
- naloxone (used to reverse the effect of opiate/opioid medicines).
- medicines used to stop opiate/opioid medicines working (e.g. naltrexone, buprenorphine).
- rifampicin (used to treat tuberculosis (TB)).
- medicines used to treat epilepsy (e.g. phenytoin, carbamazepine, phenobarbital, primidone).
- medicines that make your urine acidic (e.g. ascorbic acid (vitamin C), ammonium chloride).
- medicine used to treat diarrhoea (e.g. loperamide, diphenoxylate).
- diuretic medicine (water tablets, 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).
- cannabinoids (active components of marijuana, which may be used to reduce anxiety, reduce inflammation and pain, reduce nausea and vomiting from cancer treatment, to relax muscles in patients with multiple sclerosis, to stimulate appetite and weight gain in cancer and AIDS patients).

Concomitant use of MISYO and sedative medicines, such as benzodiazepines or related medicines, increase 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 MISYO 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.

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).

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 certain cases, your doctor may decide that it is necessary to monitor your heart with an electrocardiogram (ECG) at the start of treatment, as well as when your dose has been stabilised.

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

MISYO with food, drink and alcohol

MISYO can be taken with or without food.

Do not drink alcohol whilst taking MISYO. This is because the MISYO can make you feel sleepy and drinking alcohol will make you even sleepier.

Do not drink grapefruit juice whilst taking MISYO. This is because grapefruit juice may alter the effect of methadone.

Pregnancy, breastfeeding and fertility

If you are pregnant or breastfeeding, think you may be pregnant or are planning to have a baby, please consult your doctor, pharmacist or other health care provider for advice before taking this medicine.

Pregnancy

MISYO should not be used during pregnancy, unless deemed necessary by your doctor. However, if used during pregnancy, this should be done after a careful risk-benefit assessment by a doctor, preferably under supervision in a specialised medical centre. Dose increase up to twice a day may be necessary to maintain the effectiveness of the treatment due to changes in metabolism during the course of pregnancy.

Use during pregnancy may lead to methadone habituation and addiction of the foetus as well as to withdrawal symptoms after birth which often requires hospitalised treatment. Additionally,

the foetus may have breathing difficulties and low birth weight. There is an increased chance of stillbirths.

You should not take MISYO whilst you are in labour.

Take care if you are taking a pregnancy test as the MISYO may interfere with the results.

Breastfeeding

Talk to your doctor if you are breastfeeding or thinking of breastfeeding while you are taking MISYO. MISYO passes into the breastmilk and may affect your baby.

Mothers taking MISYO should not breastfeed their baby.

Fertility

MISYO does not appear to have an effect on female fertility.

Maintenance treatment of men with MISYO may cause sexual dysfunction and can affect ejaculate volume and sperm mobility.

Driving and using machines

Methadone may severely affect your ability to drive or use machines, during and after use. You should only start doing these activities again with the permission of your doctor.

Talk to your doctor or pharmacist if you are not sure whether it is safe for you to drive while taking MISYO.

MISYO contains sorbitol

MISYO contains 300 mg of sorbitol, liquid non-crystallising (E420) (which is equivalent to 210 mg of 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 MISYO.

MISYO contains sodium benzoate

MISYO contains 3 mg sodium benzoate in each 1 ml as preservative.

MISYO is essentially 'sodium-free'

MISYO contains less than 1 mmol sodium (23 mg) per ml, that is to say essentially 'sodium-free'.

3. How to take MISYO

You must only take MISYO by mouth. **Under no circumstances should you inject MISYO, as it may cause serious and permanent damage to your body, with the possibility of death.** The correct dosage should be extracted from the bottle by using a medicine measure, dispenser, measuring cylinder or syringe. MISYO can also be diluted with purified water, if required.

Your doctor will tell you how much MISYO 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 20 mg a day. The dose will be slowly increased over a few weeks until you show no signs of withdrawal or intoxication. The usual dose is 60 – 120 mg/day. MISYO

is usually taken once daily. Your doctor will decide what dose you need and when to reduce the dose.

Older people and people with other conditions

If you are elderly, are very ill, have liver or kidney problems, have an under active thyroid gland or have prostate problems, your doctor may monitor you more closely and may reduce your dose of MISYO.

Use in children

MISYO is not suitable for use by children.

If you take more MISYO than you should

In the event of overdosage, consult your doctor or pharmacist. If neither is available, contact the nearest hospital or poison centre.

If you take too much MISYO you can experience the following:

- difficulty breathing.
- extreme sleepiness, fainting or coma.
- pinpoint pupils.
- muscle weakness.
- cold and clammy skin.
- low blood sugar.
- slow heartbeat, low blood pressure, heart attack or shock.
- in severe cases death may occur.

If you forget to take MISYO

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 MISYO

Do not stop taking MISYO unless your doctor tells you to, as you may suffer withdrawal effects. Your doctor will tell you how to lower the dose gradually.

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

4. Possible side effects

MISYO can have side effects.

Not all side effects reported for MISYO are included in this leaflet. Should your general health worsen or if you experience any untoward effects while taking MISYO, please consult your health care provider for advice.

If any of the following happens, stop taking MISYO and tell your doctor immediately or go to the casualty department at your nearest hospital:

- 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.
- 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.
- If your breathing becomes slow and shallow.
- Worsening of the pressure inside your head if you had an injury to your head or have a brain disease. You may experience bad headaches and vomiting.
- Breathing difficulty or respiratory arrest (being unable to breathe).

- If you have asthma and it gets worse.

These are all very serious side effects. If you have them, you may have had a serious reaction to MISYO. You may need urgent medical attention or hospitalisation.

Tell your doctor if you notice any of the following:

Frequent side effects:

- Feeling or being sick
- Water retention
- Feeling high (euphoria)
- Seeing or hearing things that are not real (hallucinations)
- Sleep disturbances
- Feeling sleepy or tired
- Feeling confused
- Headache
- Blurred vision, pin point pupils, dry eyes
- Feeling of dizziness or spinning
- Constipation
- Skin rash
- Sweating
- Reduction of sex drive
- Weight increase

Less frequent side effects:

- Low levels of thyroid hormone (seen in a blood test)
- Feeling down (dysphoria)

- Feeling agitated
- Difficulty sleeping (insomnia)
- Feeling disorientated
- Fainting
- Visual disturbances
- Heart problems – slower heartbeat, feeling your heart beat (palpitations)
- Low blood pressure
- Facial flush (blushing or feeling of warmth in the face)
- Shock
- Dry nose
- Dry mouth
- Inflammation of the tongue
- Intestinal hypomotility (reduced bowel movements)
- Bile duct spasm, which may present as stomach pain
- Itching, hives (which can bleed in rare cases), rash
- Urine retention (being unable to urinate), difficulty in passing urine
- Difficulty achieving or maintaining an erection
- Disturbances or absence of menstruation
- Milky discharge from the nipples, when not breastfeeding
- Swelling of the legs (oedema of the lower extremities) or other body parts (oedema)
- Weakness
- Low body temperature

The following side effects have also been reported (frequency not known):

- Lower levels of platelets in blood, which increases the risk of bleeding or bruising, especially in patients with liver problems (seen with a blood test)

- Increased levels of the hormone, prolactin, especially with long term use (seen with a blood test)
- Loss of appetite and weight loss (anorexia)
- Blood potassium or magnesium deficiency (seen in blood tests)
- Low blood sugar
- Hearing loss

If you notice any side effects not mentioned in this leaflet, please inform your doctor or pharmacist.

Reporting of side effects

If you get side effects, talk to your doctor, pharmacist or nurse. You can also report side effects to SAHPRA via the "**6.04 Adverse Drug Reaction Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8.

By reporting side effects, you can help provide more information on the safety of MISYO.

5. How to store MISYO

Store at or below 30 °C in the original package to protect from light.

After first opening store at or below 25 °C in the original package to protect from light, for not more than 90 days.

If diluted, the diluted solution has a shelf life of 14 days when stored in PET bottles at or below 25 °C protected from light.

Store this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton, bottle after EXP. The expiry date refers to the last day of that month.

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 MISYO contains

The active substance is methadone hydrochloride. Each 1 ml of MISYO contains 10 mg of methadone hydrochloride.

The other ingredients are: citric acid monohydrate (E330), colour brilliant blue FCF (E 133), glycerol (E 422), sodium benzoate (E 211), sorbitol, liquid non-crystallising (E 420), water, purified.

What MISYO looks like and contents of the pack

MISYO is a clear blue solution.

100 ml pack size:

Type III, brown glass bottle containing 100 ml oral solution, sealed with a PP 28 screw cap with PE-liner or with a PP 28 screw cap child-resistant, tamper evident ring with embossing and PE-liner. One bottle is packed into a cardboard carton.

1000 ml pack size:

Type III, brown glass bottle containing 1000 ml oral solution, sealed with a PP 28 screw cap with PE-liner or with a PP 28 screw cap child-resistant, tamper evident ring with embossing and PE-liner. One bottle is packed into a cardboard carton.

Not all pack sizes may be marketed.

Holder of Certificate of Registration

Umsebe Healthcare

506 Sunclare Building

21 Dreyer Street, Claremont

Cape Town

7708

South Africa

Tel. 021 202 5742

Email: Info@umsebe.com

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