PROFESSIONAL INFORMATION

SCHEDULING STATUS S6

1. NAME OF THE MEDICINE

MISYO 10 mg/ml concentrate for oral solution.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1 ml of the concentrate for oral solution contains 10 mg of methadone hydrochloride.

Sugar free.

Excipients with known effects

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

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

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

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Concentrate for oral solution.

Clear blue solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Submission date: January 2022
Approved: 4 March 2022

Substitution treatment in opiate/opioid dependence in adults in conjunction with appropriate medical, social and psychological therapy.

4.2 Posology and method of administration

Posology

For oral administration only. MISYO 10 mg/ml concentrate for oral solution should be diluted by a healthcare professional before use. Please refer to section 6.6 for further instructions.

MISYO should always be taken orally with or without food.

MISYO must not be injected.

Dosage should be titrated to individual needs of patients.

Substitution treatment with methadone should be prescribed by a doctor with experience of treating opiate/opioid-dependent patients, preferably at centres that are specialised in the treatment of opiate/opioid dependency.

The dose is based on the occurrence of withdrawal symptoms and must be adjusted for each patient according to his or her individual situation and the way he or she feels. In general, after adjustment of the dose, the aim is to administer the lowest possible maintenance dose.

Adults

The standard initial dose is 20 mg methadone once daily.

The dose may be increased at 10 mg increments over a period of three weeks, usually to 70 or 80 mg. After a recommended stabilisation period of four weeks, the dose is adjusted until

the patient feels well, does not feel a need for intoxication and is without clinical signs of psychomotor function effects or abstinence symptoms. The normal dose is 60 to 120 mg of methadone per 24 hours, but some individuals may require higher doses.

The dosage must be determined based upon the clinical evaluation, supported by serum level monitoring. The recommended serum level is 600 to 1200 nmol/l (200 to 400 ng/ml). Great importance is attached to the clinical assessment.

MISYO is normally administered once daily. If administered more frequently, there will be a risk of accumulation and overdose.

Certain patients develop auto-induction, which leads to the medication being metabolised more rapidly in the body. In such cases, the dose must be adjusted upwards once or more to maintain the optimum effect.

The highest recommended dose, that rarely should be used, is 150 mg/day. The reason for this limitation is an increased frequency of QT-prolongation, Torsades de Pointes and cases of cardiac arrest within higher dose ranges (see section 4.4).

If the patient has been treated with a combined agonist/antagonist (e.g. buprenorphine), the dose should be reduced gradually when the methadone treatment is initiated. If the methadone treatment is interrupted and a switch to sublingual buprenorphine treatment is planned (especially in combination with naloxone), the methadone dose should be reduced to 30 mg/day initially to avoid withdrawal symptoms caused by buprenorphine/naloxone.

Treatment discontinuation

Treatment must be stopped if it is insufficiently effective or if the patient cannot tolerate it. The effect must be evaluated in accordance with national guidelines.

Treatment discontinuation must always be done gradually by dose reduction in weekly steps of 5 – 10 mg over several weeks to months. The dose may be reduced relatively rapidly to start with, but reduction must be slow in the final phase (from 20 mg daily and downwards).

During this period of gradual dose reduction, it is necessary to pay attention to any recurrence of withdrawal symptoms which would require a return to the previous dosage, and to any resumption of addictive behaviours.

Elderly

Caution must be exercised when treating elderly patients, as they may require a reduced dose (see section 4.4).

Patients with renal or hepatic impairment

In patients with renal disorders or mild to moderate hepatic disorders it is advisable to reduce the dose (for more information see section 4.4 and also section 4.3).

Patients with hypothyroidism or prostatic hypertrophy

Patients with hypothyroidism or prostatic hypertrophy must receive a lower initial dose.

Paediatric population

There are no data available on the use in patients under 18 years of age. Therefore, the use of MISYO is not recommended for children and adolescents (see section 4.4).

Method of administration

MISYO 10 mg/ml concentrate for oral solution must be diluted before use by a health professional and may only be used orally and under medical supervision.

4.3 Contraindications

- Hypersensitivity to methadone, benzoates, or to any of the excipients of MISYO listed in section 6.1.
- Respiratory depression.
- Use during an acute asthma attack.
- Acute alcoholism.
- Concurrent administration with monoamine oxidase (MAO) inhibitors or within 2 weeks of discontinuation of treatment with them.
- Decreased level of consciousness or head injury.
- Individuals with QT prolongation, including congenital long QT syndrome.
- MISYO should not be administered to patients with severe hepatic impairment, as it may precipitate Porto-systemic Encephalopathy in patients with severe liver damage.

4.4 Special warnings and precautions for use

It is advisable to reduce the dose for older patients, patients with renal disorders or severe chronic hepatic disorders, and patients in poor general condition.

Dependence/ tolerance

Methadone is a substance of dependence, has a long half-life and can therefore accumulate. A single dose which will relieve symptoms may, if repeated on a daily basis, lead to accumulation and possible death.

Tolerance and dependence may occur as with morphine. The risks of dependence are increased in individuals of current or past history of substance misuse disorders e.g., alcohol use disorder, opioid use disorder, drug use disorder.

MISYO can produce drowsiness and reduce consciousness although tolerance to these effects can occur after repeated use.

Withdrawal

Abrupt cessation of treatment can lead to withdrawal symptoms which, although similar to those with morphine, are less intense but more prolonged. Withdrawal of treatment should therefore be gradual.

Respiratory depression

MISYO should be used with caution in patients with asthma, chronic obstructive pulmonary disease or cor pulmonale and in patients with very limited respiratory reserve, a pre-existing impairment of respiratory function, hypoxia or hypercapnia. Even at the usual therapeutic doses for narcotics, these patients can experience a reduction in respiratory activity with a concomitant increase in airway resistance culminating in apnoea. In patients predisposed to such atopic phenomena, pre-existing asthma, skin eruptions and blood count changes (eosinophilia) can be exacerbated. Asthma may be exacerbated due to histamine release.

Due to the slow accumulation of methadone in the tissues, respiratory depression may not be fully apparent for a week or two.

The symptoms and signs of overdosage and toxicity of methadone are essentially those for morphine, though it is said that methadone has a greater respiratory depressive effect and a lesser sedative effect than an equi-analgesic dose of morphine. Toxic doses are highly

variable, regular usage giving tolerance. Pulmonary oedema is a frequent corollary of overdosage whilst the dose-related histamine-releasing property of methadone may account for at least some of the urticaria and pruritus associated with methadone administration.

Concomitant treatment with other medicines with CNS depressant activity is not advised due to the potential for CNS and respiratory depression (see also section 4.5).

Head Injury and Increased Intracranial Pressure

The respiratory depressant effects of methadone and its capacity to elevate cerebrospinal-fluid pressure may be markedly exaggerated in the presence of head injury, other intracranial lesions or a pre-existing increased intracranial pressure. Furthermore, opiates/opioids produce side effects that may obscure the clinical course of patients with head injuries. In such patients, MISYO must be used with caution and only if it is deemed essential.

MISYO has the potential to increase intracranial pressure especially where it is already raised.

Risk from concomitant use of sedative medicines such as benzodiazepines or related medicines

Concomitant use of MISYO and sedative medicines such as benzodiazepines or related medicines may result in sedation, respiratory depression, coma and death. Because of these risks, concomitant prescribing with these sedative medicines should be reserved for patients for whom alternative treatment options are not possible. If a decision is made to prescribe MISYO concomitantly with sedative medicines, the lowest effective dose should be used, and the duration of treatment should be as short as possible.

The patients should be followed closely for signs and symptoms of respiratory depression and sedation. Patients and their caregivers must be informed and made aware of these symptoms (see section 4.5).

Hepatic impairment

Caution is required in case of mild or moderate hepatic impairment, since these patients may be at risk of increased systemic exposure to methadone after multiple dosing. The usual dose of MISYO can be continued in patients with stable chronic liver disease. When there may be impaired liver function following hepatitis B or C infection or prolonged alcohol use, the MISYO dose must be monitored carefully. Particular care must be taken whenever doses of over 50 mg are prescribed.

Renal impairment

Caution should be exercised in the use of MISYO in patients with renal impairment. The dose interval should be lengthened to a minimum of 32 hours if the glomerular filtration rate (GFR) is 10 – 50 ml/min and to a minimum of 36 hours if the GFR is lower than 10 ml/min.

Gastrointestinal motility

Methadone may cause troublesome constipation, which is particularly dangerous in patients with severe hepatic impairment, and measures to avoid constipation should be initiated early.

Hypoglycaemia

Hypoglycaemia has been observed in the context of methadone overdose or dose escalation. Regular monitoring of blood sugar is recommended during dose escalation (see section 4.8 and section 4.9).

Adrenal insufficiency

Opiate/opioid analgesics may cause reversible adrenal insufficiency requiring monitoring and glucocorticoid replacement therapy. Symptoms of adrenal insufficiency may include nausea, vomiting, loss of appetite, fatigue, weakness, dizziness, or low blood pressure.

Decreased sex hormones and increased prolactin

Long-term use of opiate/opioid analgesics may be associated with decreased sex hormone levels and increased prolactin. Symptoms include decreased libido, impotence or amenorrhea.

Neonates/children

As there is a risk of greater respiratory depression in neonates the use of MISYO in children and adolescents under 18 years of age is not recommended owing to a lack of clinical findings on efficacy and safety.

Further warnings

Babies born to mothers receiving MISYO may suffer withdrawal symptoms.

MISYO should be used with caution in patients with convulsive disorders, hypothyroidism, adrenocortical insufficiency, prostatic hyperplasia, hypotension, shock, inflammatory or obstructive bowel disorders or myasthenia gravis.

MISYO should be used with caution and in reduced dosage in patients who are concomitantly using other narcotic analgesics, general anaesthetics, phenothiazines, other tranquillisers, sedative hypnotics, tricyclic antidepressants, and other CNS depressants (including alcohol) (see 4.5 Interactions with other medicinal products and other forms of interaction).

Cases of QT interval prolongation and *torsades de pointes* have been reported during treatment with methadone, particularly at high doses (>100 mg/day). MISYO should be administered with caution to patients at risk for development of prolonged QT interval, e.g. in case of:

- history of cardiac conduction abnormalities.
- advanced or ischaemic heart disease.
- liver disease.
- family history of sudden death.
- electrolyte abnormalities, i.e. hypokalaemia, hypomagnesaemia.
- concomitant treatment with substances that have a potential for QT-prolongation.
- concomitant treatment with substances which may cause electrolyte abnormalities.
- concomitant treatment with cytochrome P450 CYP3A4 inhibitors (see section 4.5).

In patients treated with a combined agonist/antagonist (e.g. buprenorphine), the dose should be reduced gradually when the MISYO treatment is initiated. If the MISYO treatment is interrupted and a switch to sublingual buprenorphine treatment is planned (especially in combination with naloxone), the MISYO dose should be reduced to 30 mg/day initially to avoid withdrawal symptoms caused by buprenorphine/naloxone.

In patients with recognised risk factors for QT-prolongation, or in case of concomitant treatment with substances that have a potential for QT-prolongation, ECG monitoring is recommended prior to MISYO treatment, with a further ECG test at dose stabilisation. ECG monitoring is recommended, in patients without recognised risk factors for QT-prolongation, before dose titration above 100 mg/day and at seven days after titration.

Caution should be exercised in patients who are concurrently taking central nervous system (CNS) depressants.

Excipients

MISYO 10 mg/ml concentrate for oral solution contains 300 mg of sorbitol, liquid non-crystallising (E420) (which is equivalent to 210 mg of sorbitol), which may have a laxative effect. The additive effect of concomitantly administered products containing sorbitol (or fructose) and dietary intake of sorbitol (or fructose) should be taken into account. Patients with the rare hereditary condition of sorbitol / maltitol / lactitol / intolerance should not take MISYO.

MISYO 10 mg/ml concentrate for oral solution contains less than 1 mmol sodium (23 mg) per ml, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicines and other forms of interaction

Pharmacokinetic interactions

P-glycoprotein inhibitors

Methadone is a substrate of p-glycoprotein; all medicines that inhibit P-glycoprotein (e.g. quinidine, verapamil, ciclosporin), may therefore raise the serum concentration of methadone. The pharmacodynamic effect of methadone may also increase because of increased blood brain barrier passage.

CYP3A4-enzyme inducers

Methadone is a substrate of CYP3A4 (see section 5.2). By induction of CYP3A4, clearance of methadone will increase and the plasma levels decrease. Inducers of this enzyme (barbiturates, carbamazepine, phenytoin, nevirapine, rifampicin, efavirenz, amprenavir, spironolactone, dexamethasone, *Hypericum perforatum* (St John's Wort)), may induce hepatic metabolism. For instance, after three weeks' treatment with 600 mg efavirenz daily, the mean

maximal plasma concentration and AUC decreased by 48 % and 57 % respectively, in patients treated with methadone (35 – 100 mg daily).

The consequences of enzyme induction are more marked if the inducer is administered after treatment with methadone has begun. Abstinence symptoms have been reported following such interactions and hence, it may be necessary to increase the MISYO dose. If treatment with a CYP3A4 inducer is interrupted, the MISYO dose should be reduced.

Co-administration of MISYO with metamizole, which is an inducer of metabolising enzymes including CYP2B6 and CYP3A4 may cause a reduction in plasma concentrations of methadone with potential decrease in clinical efficacy. Therefore, caution is advised when metamizole and MISYO are administered concurrently; clinical response and/or medicine levels should be monitored as appropriate.

CYP3A4-enzyme inhibitors

Methadone is a substrate of CYP3A4 (see section 5.2). By inhibition of CYP3A4 clearance of methadone is lowered. Concomitant administration of CYP3A4 inhibitors (e.g. cannabinoids, clarithromycin, delavirdine, erythromycin, ciprofloxacin, fluconazole, grapefruit juice, cimetidine, itraconazole, ketoconazole, fluoxetine, fluvoxamine, nefazodone and telithromycin) may result in increased plasma concentrations of methadone. A 40 – 100 % increase of the quote between the serum levels and the methadone dose has been shown with concomitant fluvoxamine treatment. If these medicinal products are prescribed to patients on MISYO maintenance treatment, one should be aware of the risk of overdose. Dose adjustment may be necessary.

Products that affect the acidity of the urine

Methadone is a weak base. Acidifiers of the urine (such as ammonium chloride and ascorbic acid) may increase the renal clearance of methadone. Patients that are treated with MISYO are recommended to avoid products containing ammonium chloride.

Concomitant HIV infection treatment

Some protease inhibitors (amprenavir, nelfinavir, abacavir, lopinavir/ritonavir and ritonavir/saquinavir) seem to decrease the serum levels of methadone. When ritonavir is administered alone, a two-fold AUC of methadone has been observed. The plasma levels of zidovudine (a nucleoside analogue) increase with methadone use after both oral and intravenous administration of zidovudine. This is more noticeable after oral than after intravenous use of zidovudine. These observations are likely caused by inhibition of zidovudine glucuronidation, and therefore decreased clearance of zidovudine. During treatment with MISYO, patients must be carefully monitored for signs of toxicity caused by zidovudine, which may require a reduction in the zidovudine dose. Because of mutual interactions between zidovudine and methadone (zidovudine is a CYP3A4 inducer), typical opiate/opioid abstinence symptoms may develop during concomitant use (headache, myalgia, fatigue and irritability).

Didanosine and stavudine

Methadone delays the absorption and increases the first pass metabolism of stavudine and didanosine, which results in a decreased bioavailability of stavudine and didanosine.

Desipramine

MISYO may double the serum levels of desipramine.

Pharmacodynamic interactions

Opiate/opioid antagonists

Naloxone and naltrexone counteract the effects of methadone and induces abstinence. Similarly, buprenorphine and pentazocine may precipitate withdrawal symptoms.

CNS depressants

Medicines with a sedative effect on the central nervous system may result in increased respiratory depression, hypotension, strong sedation or coma; therefore, it may be necessary to reduce the dose of one or both of the medicines. With MISYO treatment, the slowly eliminated substance methadone, gives rise to a slow tolerance development, and every dose increase may after 1 – 2 weeks give rise to symptoms of respiratory depression. The dose adjustments must therefore be made with caution and the dose increased gradually and with careful observation.

Anaesthetics, sedative-hypnotics (including barbiturates, chloral hydrate and chlormethiazole), anxiolytics phenothiazines, antipsychotics and tricyclic antidepressants may increase the general depressant effects of methadone when used concomitantly (see 4.4 Special warnings and precautions for use). Antipsychotics may enhance the sedative effects and hypotensive effects of MISYO.

Sedative medicines such as benzodiazepines or related medicines

The concomitant use of opiates/opioids with sedative medicines such as benzodiazepines or related medicines increases the risk of sedation, respiratory depression, coma and death because of additive CNS depressant effect. The dose and duration of concomitant use should be limited (see section 4.4).

Peristalsis inhibition

Concomitant use of MISYO and peristalsis inhibiting medicines (loperamide and diphenoxylate) may result in severe obstipation and increase the CNS depressant effects.

Opiate/opioid analgesics, in combination with antimuscarinics, may result in severe obstipation or paralytic ileus, especially in long-term use.

QT-prolongation

MISYO should not be combined with medicines that may prolong the QT interval such as antidysrhythmics (sotalol, amiodarone, and flecainide), antipsychotics (thioridazine, haloperidol, sertindole, and phenotiazines), antidepressants (paroxetine, sertraline) or antibiotics (erythromycin, clarithromycin).

Serotonergic medicines

Serotonergic syndrome may occur with concomitant administration of MISYO with pethidine, monoamine oxidase (MAO) inhibitors and serotonin medicines such as Selective Serotonin Re-uptake Inhibitor (SSRI), Serotonin Norepinephrine Re-uptake Inhibitor (SNRI) and tricyclic antidepressants (TCAs). The symptoms of serotonin syndrome may include mental-status changes, autonomic instability, neuromuscular abnormalities, and/or gastrointestinal symptoms.

MAO-inhibitors

Concomitant administration of MAO-inhibitors may result in reinforced CNS-inhibition, serious hypotonia and or apnoea. MISYO should not be combined with MAO-inhibitors and two weeks after such treatment (see section 4.3).

Analgesics

Maintenance patients on a stable dose of MISYO who experience physical trauma, postoperative pain or other causes of acute pain cannot be expected to derive analgesia from their stable dose of methadone regimens. Such patients should be given analgesics, including opiates/opioids that would be indicated in other patients experiencing similar nociceptive

stimulation. Due to the opiate/opioid tolerance induced by MISYO, when opiates/opioids are required for management of acute pain in methadone patients, somewhat higher and/or more frequent doses will often be required than would be the case for other, non-tolerant patients.

Diagnostic / Lab Interactions

Gastric emptying studies

MISYO may delay gastric emptying, thereby invalidating test results.

Hepatobiliary imaging using technetium Tc 99m disofenin

Delivery of technetium Tc 99m disofenin to the small bowel may be prevented because MISYO may cause constriction of the sphincter of Oddi and increased biliary tract pressure; these actions result in delayed visualization and thus resemble obstruction of the common bile duct.

Cerebrospinal fluid pressure

Cerebrospinal fluid pressure may be increased; effect is secondary to respiratory depression-induced carbon dioxide retention.

Plasma amylase or lipase levels

Plasma amylase or lipase levels may be increased because MISYO can cause contractions of the sphincter of Oddi and increased biliary tract pressure; the diagnostic utility of determination of these enzymes may be compromised for up to 24 hours after the medication has been given.

Urine tests

MISYO may modify urine tests and give a positive result in doping control.

Pregnancy tests

MISYO may interfere with urine testing for pregnancy.

4.6 Fertility, pregnancy and lactation

Pregnancy

Methadone administered to pregnant women for the management of opiate/opioid addiction has the potential for several adverse effects on the foetus and the neonate. Withdrawal symptoms/respiratory depression may occur in neonates of mothers who were treated with methadone chronically during pregnancy. Studies in animals provided evidence of reproductive toxicity (see section 5.3). However, limited data on the use of methadone in pregnancy in humans show no elevated risk of congenital abnormalities.

MISYO should not be administered to pregnant women, because of possible adverse effects on the foetus and neonate including respiratory depression, low birth weight, neonatal withdrawal syndrome and increased rate of stillbirths. However, if maternal MISYO substitution therapy is strongly indicated, careful monitoring is required.

It may be necessary to increase the dose of MISYO if withdrawal symptoms develop. Increased clearance and reduced plasma levels have been reported during pregnancy. Considering the well-being of the foetus, it may be advisable to split up the daily dose in order to prevent high peak plasma concentrations and to compensate the accelerated degradation of methadone, thus preventing withdrawal symptoms. Dose reduction or withdrawal during pregnancy must always be carried out under careful monitoring of the mother and only after a stringent risk/benefit assessment. Medicine withdrawal of the neonate must be carried out at an adequate intensive care unit for children, as treatment with MISYO may lead to habituation and addiction of the foetus as well as to withdrawal symptoms in the neonate, which require treatment. Approximately 60 – 80 % of the neonates require hospitalised treatment due to the neonatal abstinence syndrome. Dose adjustment (especially dose reduction) may be

necessary within 1 – 2 weeks postnatal. The use of MISYO just before and during birth is advised against because of the risk of neonatal respiratory depression.

Breastfeeding

Methadone is excreted in breastmilk and MISYO should not be used during lactation.

Fertility

Methadone does not appear to impair human female fertility.

Studies in men on methadone maintenance programmes have shown that methadone reduces serum testosterone and markedly depresses the ejaculate volume and sperm motility. The sperm counts of methadone subjects were twice that of controls but this reflected the lack of dilution from seminal secretions.

4.7 Effects on ability to drive and use machines

MISYO has a major influence on the ability to drive and use machines, during and after treatment, as it may cause drowsiness and reduce alertness. The time after which such activities may be safely resumed is extremely patient-dependent and must be decided by the medical practitioner.

4.8 Undesirable effects

The adverse effects of methadone are most commonly nausea and vomiting, that is observed in approximately 20 % of the patients that go through methadone outpatient treatment, where the medicinal control is often unsatisfactory.

Long term use of MISYO may lead to morphine-like dependence.

The most serious adverse effect of methadone is respiratory depression, which may emerge during the stabilisation phase. Apnoea, shock and cardiac arrest have occurred.

Adverse reactions listed below are classified according to frequency and system organ class. These reactions are more frequently observed in non-opiate/opioid-tolerant individuals.

System organ class (MedDRA)	**Frequency**	**Adverse event**
Blood and lymphatic system disorders	Not known	Reversible thrombocytopenia has been reported in opiate/opioid-dependent patients with chronic hepatitis
Endocrine disorders	Less frequent	Hypothyroidism
	Not known	Raised prolactin levels with long-term administration
Metabolism and nutrition disorders	Frequent	Fluid retention
	Not known	Anorexia, hypokalaemia, hypomagnesaemia, hypoglycaemia
Psychiatric disorders	Frequent	Euphoria, hallucinations, sleep disturbances
	Less frequent	Dysphoria, agitation, insomnia, disorientation
Nervous system disorders	Frequent	Sedation, dizziness, confusion, headache
	Less frequent	Syncope
Eye disorders	Frequent	Blurred vision, miosis, dry eyes
	Less frequent	Visual disturbances
	Frequent	Vertigo

Ear and labyrinth disorders	Not known	Hearing loss
Cardiac disorders	Less frequent	Bradycardia, palpitations, cases of prolonged QT interval and torsade de pointes have been reported, especially with high doses of methadone
Vascular disorders	Less frequent	Facial flush, hypotension (particularly at high doses), shock
Respiratory, thoracic and mediastinal disorders	Less frequent	Pulmonary oedema, exacerbation of asthma, dry nose, respiratory depression (particularly at high doses), respiratory arrest
Gastrointestinal disorders	Frequent	Nausea, vomiting, constipation
	Less frequent	Xerostomia, glossitis, intestinal hypomotility (ileus)
Hepatobiliary disorders	Less frequent	Bile duct dyskinesia
Skin and subcutaneous tissue disorders	Frequent	Transient rash, sweating
	Less frequent	Pruritus, urticaria, other rash and in very uncommon cases bleeding urticaria
Renal and urinary disorders	Less frequent	Urinary retention, anti-diuretic effect
Reproductive system and breast disorders	Frequent	Decreased libido
	Less frequent	Reduced potency, galactorrhoea, dysmenorrhoea and amenorrhoea

General disorders and administration site condition	Frequent	Fatigue, drowsiness
	Less frequent	Oedema of the lower extremities (limbs), asthenia, oedema, hypothermia
Investigations	Frequent	Weight increase

In long term use of methadone, as for maintenance treatment, the undesirable effects diminish successively and progressively during a period of several weeks however, constipation and perspiration often remain.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare providers are asked to report any suspected adverse reactions to SAHPRA via the "6.04 Adverse Drug Reactions Reporting Form", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

Symptoms

Serious overdose is characterised by respiratory depression, extreme somnolence progressing to stupor or coma, maximally constricted pupils, skeletal muscle flaccidity, cold and clammy skin and sometimes bradycardia and hypotension. Hypoglycaemia has been reported. In severe overdose, particularly by the intravenous route, apnoea, circulatory collapse, cardiac arrest and death may occur.

Treatment

A patent airway and assisted or controlled ventilation must be assured. Narcotic antagonists may be required, but it should be remembered that methadone is a long-acting depressant

(36 to 48 hours), whereas antagonists act for 30 to 60 minutes, so that treatment with the latter must be repeated as needed. An antagonist should not be administered, however, in the absence of clinically significant respiratory or cardiovascular depression. The administration of naloxone is advised.

Oxygen, intravenous fluids, vasopressors and other supportive measures should be employed as indicated. In a person physically dependent on narcotics, administration of the usual dose of a narcotic antagonist will precipitate an acute withdrawal syndrome; use of the antagonist in such a person should be avoided if possible, but if it must be used to treat serious respiratory depression if should be administered with great care.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacological classification: 2.9 Other analgesics

Pharmacotherapeutic group: Medicine used in opioid dependence

ATC code: N07BC02

Mechanism of action

Methadone is a narcotic analgesic that belongs to the same group as morphine. Methadone is a strong opiate/opioid agonist with actions predominantly at the μ receptor. The analgesic activity of the racemate is almost entirely due to the *l*-isomer, which is at least 10 times more potent as an analgesic than the *d*-isomer. The *d*-isomer lacks significant respiratory depressant activity, but does have anti-tussive effects. Methadone also has some agonist actions at the κ and δ opiate/opioid receptors.

Methadone operates in a similar way to morphine, but has a less sedative effect. The use of methadone can reduce or eliminate the effect of other opiates/opioids.

Pharmacodynamic effects

These actions result in analgesia, depression of respiration, suppression of cough, nausea and vomiting (*via* an effect of the chemoreceptor trigger zone) and constipation. An effect on the nucleus of the oculomotor nerve, and perhaps on opiate/opioid receptors in the pupillary muscles, causes pupillary constriction.

All these effects are reversible by naloxone with pA_2 value similar to its anti-antagonism of morphine. Like many basic substances, methadone enters mast cells and releases histamine by a non-immunological mechanism. It causes a dependence syndrome of the morphine type.

5.2 Pharmacokinetic properties

Absorption

Methadone is one of the more lipid-soluble opioids and is well absorbed from the gastrointestinal tract, but undergoes fairly extensive first-pass metabolism. The bioavailability is above 80 %. Steady state concentrations are reached within 5 – 7 days.

Distribution

Methadone is bound to albumin and other plasma proteins and to tissue proteins (probably lipoproteins). The concentrations in the lung, liver and kidneys are much higher than in blood. The pharmacokinetics of methadone is unusual, in that there is extensive binding to tissue proteins and fairly slow transfer between some parts of this tissue reservoir and the plasma. Methadone is secreted in sweat and found in saliva, breast milk and in the cord blood.

Biotransformation

Methadone is metabolised in the liver, mainly by N-demethylation and cyclisation. The metabolism of methadone is catalysed primarily by CYP3A4, but CYP2D6 and CYP2B6 are

also involved, to a smaller extent. Metabolism is mainly N-demethylation, which produces the most important metabolites: 2-ethylidine, 1,5-dimethyl-3,3-diphenylpyrrolidine (EDDP) and 2-ethyl-5-methyl-3,3-diphenyl-1-pyrrolidine (EMDP), which are both inactive. Hydroxylation to methadol succeeded by N-demethylisation to normethadol also occurs to some extent. Other metabolic reactions also occur, and at least eight other metabolites are known.

Elimination

The half-life after a single oral dose is 10 – 25 hours, partly reflecting distribution into tissue stores, as well as metabolic and renal clearance. With regular doses, the tissue reservoir is already partly filled and so the half-life is extended to 13 – 55 hours reflecting only clearance.

Plasma clearance is around 2 ml/min/kg. About 20 to 60 % of the dose is eliminated in urine over 24 hours (about 33 % in unmodified form; about 43 % as EDDP and about 5 – 10 % as EMDP).

Methadone and its metabolites are excreted to varying degree in the faeces and urine. Excretion of methadone is markedly enhanced by the acidification of the urine. About 30 % of the dose is eliminated in faeces, but this percentage will normally be reduced at higher doses. About 75 % of overall elimination is unconjugated.

Special populations

There are no significant differences in the pharmacokinetics between men and women. The clearance of methadone is decreased only to some extent in the elderly (>65 years).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Citric acid monohydrate (E330), colour brilliant blue FCF (E 133), glycerol (E422), sodium benzoate (E211), sorbitol, liquid non-crystallising (E420), water, purified.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months.

Shelf life after first opening container: 90 days.

Shelf life after dilution: 14 days.

6.4 Special precautions for storage

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.

Once diluted to a concentration of 1 mg/ml or 5 mg/ml it has a shelf life of 14 days when stored in PET bottles at or below 25 °C protected from light.

Keep out of the sight and reach of children.

6.5 Nature and contents of container

Type III, brown glass bottle containing 100 ml concentrate for 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 in to a cardboard carton.

Type III, brown glass bottle containing 1000 ml concentrate for 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 in to a cardboard carton.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

MISYO 10 mg/ml concentrate for oral solution is supplied in dispensing packs which are only to be used by healthcare professionals.

MISYO 10 mg/ml concentrate for oral solution should be diluted with purified water to produce either a 1 mg/ml or a 5 mg/ml methadone hydrochloride oral solution before being used by the patient.

The 1 mg/ml methadone hydrochloride oral solution is prepared by diluting 1 part of the concentrate for oral solution with 9 parts of purified water (10-fold dilution).

The 5 mg/ml methadone hydrochloride oral solution is prepared by diluting 1 part of the concentrate for oral solution with 1 part of purified water (2-fold dilution).

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Umsebe Healthcare

Unit 20, Sunclare Building, 3rd Floor

21 Dreyer Street, Claremont

Cape Town

7708

South Africa

8. REGISTRATION NUMBER

55/2.9/0741

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

9 November 2021

10. DATE OF REVISION OF THE TEXT

4 March 2022

NAMIBIA:

MISYO 10 mg/ml concentrate for oral solution: Reg. No.: 21/2.10/0088 NS4