SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

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.
Excipient with known effect
Each 1 ml of the concentrate for oral solution contains 300.00 mg of sorbitol, liquid non-crystallising (E420) (which is equivalent to 210.00 mg of sorbitol) and 3.0 mg sodium benzoate (E211).
Each 1 ml of the concentrate for oral solution contains 0.478 mg (0.021 mmol) sodium.

For the 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

Substitution therapy for maintenance of opioid dependence in adults in conjunction with appropriate medical, social and psychosocial care.

4.2 Posology and method of administration

Posology

For oral administration only. This product should be diluted by a healthcare professional before use. Please refer to section 6.6 for further instructions.
This medicinal product should always be taken orally with or without food.

This product must not be injected.

Dosage should be titrated to individual needs of patients. Local guidance may differ from the posology described hereafter and should be followed.

Substitution treatment with methadone should be prescribed by a doctor with experience of treating opiate/opioid-dependent patients, preferably at centres that have specialised in the treatment of opiate/opioid dependency.
The dose is administered exclusively by the doctor or someone appointed by the doctor. The amount to be taken is never measured by the patient. The appropriate dose is given to the patient for immediate use only and used as directed by the doctor.

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
In general the initial dose will be between 10-30 mg. In cases where tolerance to opioids is high, the normal initial dose will be between 25-40 mg. In reaching the maintenance treatment it is recommended that the dose is increased by maximum 10 mg at a time. The majority of individuals in maintenance treatment will require 60-120 mg per day for an effective and safe treatment, some may however need a higher dosage. The dosage should be determined based upon the clinical evaluation.

Methadone is normally administered once daily. If administered more frequently, there will be a risk of accumulation and overdose. The highest recommended dose, that rarely should be used, is 150 mg/day (unless national guidelines recommend otherwise). 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 discontinuation must always be done very gradually, by weekly steps of 5-10 mg over several weeks to months. 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.

Older people
In older patients it is recommended to reduce the 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).

Paediatric population
There are no data available on the use in patients under 18 years of age. Therefore the use of Misyo 10 mg/ml concentrate for oral solution is not recommended for children and adolescents (see section 4.4).

<u>Method of administration</u>

Misyo 10 mg/ml concentrate for oral solution may only be used orally and under medical supervision.

The patient receives the required dose from the doctor or someone appointed by the doctor and takes it immediately. The required amount is measured exclusively by the doctor or the person appointed by the doctor.

Take-home must be prescribed by the doctor.
Take-home prescription is not acceptable if the doctor's tests and findings reveal that the patient consumes substances that are dangerous when combined with the substitution treatment, taking into account the development of tolerance, a stable maintenance dose has not yet been reached, or there is substance abuse by the patient.

Misyo 10 mg/ml concentrate for oral solution contains sorbitol which may affect the bioavailability of methadone in some individuals. In these individuals switching between Misyo 10 mg/ml concentrate for oral solution and other methadone products which do not contain sorbitol can result in clinically relevant changes in plasma methadone levels.

4.3 Contraindications

- Hypersensitivity to the active substance, benzoates, or to any of the excipients listed in section 6.1.
- Use during an acute asthma attack
- Acute alcoholism
- Concurrent administration with monoamino oxidase (MAO) inhibitors or within 2 weeks of discontinuation of treatment with them
- Absence of dependence on opioid substances
- Individuals with QT prolongation, including congenital long QT syndrome;
- As with all opioid analgesics, this product should not be administered to patients with severe hepatic impairment as it may precipitate Porto-systemic Encephalopathy in patients with severe liver damage.

Use during labour is not recommended, the prolonged duration of action increases the risk of neonatal respiratory depression.

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.

*Opioid Use Disorder (abuse and dependence)*Methadone is an opioid analgesic and is highly addictive in its own right. It 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.

As with other opioids, tolerance, physical, and/or psychological dependence may develop upon repeated administration of methadone. Methadone can produce drowsiness and reduce consciousness although tolerance to these effects can occur after repeated use.

Abuse or intentional misuse of Misyo 10 mg/ml concentrate for oral solution may result in overdose and/or death.
The risk of developing Opioid Use Disorder (OUD) is increased in patients with a personal or a family history (parents or siblings) of substance use disorders (including alcohol use disorder), in current tobacco users or in patients with a personal history of other mental health disorders (e.g., major depression, anxiety and personality disorders).

Patients will require monitoring for signs of drug-seeking behaviour (e.g., too early requests for refills). This includes the review of concomitant opioids and psycho-active drugs (like benzodiazepines). For patients with signs and symptoms of OUD, consultation with an addiction specialist should be considered.

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
Like other opioids, methadone 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 pruritis associated with methadone administration.
Concomitant treatment with other agents with CNS depressant activity is not advised due to the potential for CNS and respiratory depression (see also section 4.5).

Sleep-related breathing disorders
Opioids can cause sleep-related breathing disorders including central sleep apnoea (CSA) and sleep-related hypoxemia. Opioid use increases the risk of CSA in a dose-dependent fashion. In patients who present with CSA, consider decreasing the total opioid dosage.

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, opioids produce side effects that may obscure the clinical course of patients with head injuries. In such patients, methadone must be used with caution and only if it is deemed essential.
Methadone 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 drugs
Concomitant use of Misyo 10 mg/ml concentrate for oral solution and sedative medicines such as benzodiazepines or related drugs 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 10 mg/ml concentrate for oral solution 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. In this respect, it is strongly recommended to inform patients and their caregivers to be 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 methadone 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, methadone 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 methadone 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.

Gastro-intestinal motility
Opioids including methadone may cause troublesome constipation, which is particularly dangerous in patients with severe hepatic impairment, and measures to avoid constipation should be initiated early.

Hepatobiliary disorders
Methadone may cause dysfunction and spasm of the sphincter of Oddi, increasing the risk of biliary tract symptoms and pancreatitis. Therefore, methadone has to be administered with caution in patients with pancreatitis and diseases of the biliary tract.

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
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 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 methadone in children and adolescents under 18 years of age is not recommended owing to a lack of clinical findings on efficacy and safety.

There are reports of neonates and children exposed to methadone during pregnancy developing visual disorders, including reduced visual acuity, strabismus and nystagmus. The causal relationship to methadone in isolation has not been established as factors such as other drugs taken during pregnancy e.g. benzodiazepines, intake of alcohol, and drugs used to treat neonatal abstinence syndrome e.g. phenobarbital, could play a role in the adverse reactions seen. However, there is sufficient evidence to suggest that an association is possible and therefore consideration of this risk should be taken during prescribing decisions.

Further warnings

Babies born to mothers receiving methadone may suffer withdrawal symptoms.

Methadone 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.

Methadone 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). Methadone 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 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.

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 methadone treatment, with a further ECG test at dose stabilisation.
ECG monitoring is recommended, in patients without recognised risk factors fro 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
This medicine contains 300.00 mg of sorbitol, liquid non-crystallising (E420) (which is equivalent to 210.00 mg of sorbitol).
The additive effect of concomitantly administered products containing sorbitol (or fructose) and dietary intake of sorbitol (or fructose) should be taken into account.

The content of sorbitol in medicinal products for oral use may affect the bioavailability of other medicinal products for oral use administered concomitantly.
Patients with hereditary fructose intolerance (HFI) should not take/be given this medicinal product.

This medicine contains 3.00 mg sodium benzoate (E 211) in each 1 ml.
Although this medicine is not intended for use in newborns, it is important to know that an increase in bilirubinaemia following bilirubin displacement from albumin due to the presence of benzoate, may increase neonatal jaundice which may develop into kernicterus (non-conjugated bilirubin deposits in the brain tissue).

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

4.5 Interaction with other medicinal products and other forms of interaction

Pharmacokinetic interactions
P-glycoprotein inhibitors: Methadone is a substrate of p-glycoprotein; all medicinal products that inhibit P-glycoprotein (e.g. qunidine, 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, spirononlactone, 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 methadone dose. If treatment with a CYP3A4 inducer is interrupted, the methadone dose should be reduced.
Co-administration of methadone 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 methadone are administered concurrently; clinical response and/or drug 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 methadone maintenance treatment, one should be aware of the risk of overdose.
Cannabidiol: Concomitant administration of cannabidiol may result in increased plasma concentrations of methadone
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 methadone 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 methadone, patients must be carefully monitored for signs of toxicity caused by zidovudine, why it may be necessary to reduce the dose of zidovudine. Because of mutual interactions between zidovudine and methadone (zidovudine is a CYP3A4 inducer), typical 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.
Methadone may double the serum levels of desipramine.

Pharmacodynamic interactions
Opioid antagonists: Naloxone and Naltrexone counteracts the effects of methadone and induces abstinence. Similarly buprenorphine may precipitate withdrawal symptoms.
CNS depressants: Medicinal products 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 medicinal products. With methadone treatment, the slowly eliminated substance methadone, give 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 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 methadone.
Sedative medicines such as benzodiazepines or related drugs: The concomitant use of opioids with sedative medicines such as benzodiazepines or related drugs 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).
Gabapentinoids: The concomitant use of opioids and gabapentinoids (gabapentin and pregabalin) increases the risk of opioid overdose, respiratory depression, and death.
Peristalsis inhibition: Concomitant use of methadone and peristalsis inhibiting medicinal products (loperamide and diphenoxylate) may result in severe obstipation and increase the CNS depressant effects. Opioid analgesics, in combination with antimuscarinics, may result in severe obstipation or paralytic ileus, especially in long-term use.
QT-prolongation: Methadone should not be combined with medicinal products that may prolong the QT interval such as antiarrhytmics (sotalol, amiodarone, and flecainide), antipsychotics (thioridazine, haloperidol, sertindole, and phenotiazines), antidepressants (paroxetine, sertraline) or antibiotics (erythromycin, clarithromycin).
Serotonergic drugs: Serotonergic syndrome may occur with concomitant administration of methadone with pethidine, monoamine oxidase (MAO) inhibitors and serotonin agents 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. Methadone 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 methadone 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 opioids that would be indicated in other patients experiencing similar nociceptive stimulation. Due to the opioid tolerance induced by methadone, when 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
Opioid analgesics 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 opioid analgesics 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 opioid analgesics 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
Methadone may modify urine tests and give a positive result in doping control.

Pregnancy tests
Methadone may interfere with urine testing for pregnancy.

4.6 Fertility, pregnancy and lactation

Pregnancy
Methadone administered to pregnant women for the management of 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). Some observational studies have reported congenital malformations and neurodevelopmental impairment in children born to women treated with methadone for opioid use disorder during pregnancy. However, due to study limitations and confounding by maternal, familial and socioenvironmental factors associated with opioid use disorders no conclusions can be drawn regarding the contribution of methadone.
A careful risk/benefit assessment should be made before administration 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, adequate substitution and prevention of withdrawal symptoms during pregnancy must be ensured in order to minimize damage to the foetus.
It may be necessary to increase the dose of methadone 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 drug withdrawal during pregnancy must always be carried out under careful monitoring of the mother and only after a stringent risk/benefit assessment. Drug withdrawal of the neonate must be carried out at an adequate intensive care unit for children as treatment with methadone 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 methadone oral solution just before and during birth is advised against because of the risk of neonatal respiratory depression.

Reports of visual disorders have been reported in neonates and children following exposure to methadone during pregnancy. Although other factors have also been present, there is sufficient evidence to suggest that an association is possible (see section 4.4).

Breast-feeding
Methadone is excreted in breastmilk at low levels. The decision to recommend breast-feeding should take into account clinical specialist advice and consideration should be given to whether the woman is on a stable maintenance dose of methadone and any continued use of illicit substances. If breastfeeding is considered, the dose of methadone should be as low as possible. Prescribers should advise breastfeeding women to monitor the infant for sedation and breathing difficulties and to seek immediate medical care if this occurs. Although the amount of methadone excreted in breast milk is not sufficient to fully suppress withdrawal symptoms in breast-fed infants, it may attenuate the severity of neonatal abstinence syndrome. If it is necessary to discontinue breastfeeding it should be done gradually, as abrupt weaning could increase withdrawal symptoms in the infant.

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

Methadone has 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 physician.

This medicine can impair cognitive function and can affect a patient's ability to drive safely. This class of medicine is in the list of drugs included in regulations under 5a of the Road Traffic Act 1988. When prescribing this medicine, patients should be told:

- The medicine is likely to affect your ability to drive
- Do not drive until you know how the medicine affects you
- It is an offence to drive while under the influence of this medicine
- However, you would not be committing an offence (called 'statutory defence') if:
  - The medicine has been prescribed to treat a medical or dental problem and
  - You have taken it according to the instructions given by the prescriber and in the information provided with the medicine and
  - It was not affecting your ability to drive safely

Details regarding a new driving offence concerning driving after drugs have been taken in the UK may be found here: https://www.gov.uk/drug-driving-law

4.8 Undesirable effects

The adverse effects of methadone are generally the same as with other opioids, 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 methadone may lead to morphine-like dependence. The abstinence syndromes are similar to the ones observed with morphine and heroine, however less intense, but more long-lasting.
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-opioid-tolerant individuals. Frequency groupings are defined according to the following convention: very common (≥ 1/10), common (≥ 1 /100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000), very rare (< 1/10,000), not known (cannot be estimated from the available data).

System organ class (MedDRA)	**Frequency**	**Adverse event**
Blood and lymphatic system disorders	Not known	Reversible thrombocytopenia has been reported in opioid-dependent patients with chronic hepatitis.
Endocrine disorders	Not known	Raised prolactin levels with long-term administration
Metabolism and nutrition disorders	Common	Fluid retention
	Not known	Anorexia, hypokalaemia, hypomagnesaemia, hypoglycaemia
Psychiatric disorders	Common	Euphoria, hallucinations
	Uncommon	Dysphoria, agitation, insomnia, disorientation, decreased libido
	Not known	Dependence
Nervous system disorders	Common	Sedation
	Uncommon	Headache, syncope
Eye disorders	Common	Blurred vision, miosis, dry eyes
	Not known	Nystagmus[1], strabismus[1], visual acuity reduced[1]
Ear and labyrinth disorders	Common	Vertigo
	Not known	Hearing loss

Cardiac disorders	Rare	Bradycardia, palpitations, cases of prolonged QT interval and torsade de pointes have been reported, especially with high doses of methadone.
Vascular disorders	Uncommon	Facial flush, hypotension
	Rare	Shock
Respiratory, thoracic and mediastinal disorders	Uncommon	Pulmonary oedema, exacerbation of asthma, dry nose, respiratory depression particularly with large doses
	Rare	Respiratory arrest
	Not known	Central sleep apnoea syndrome
Gastrointestinal disorders	Very common	Nausea, vomiting
	Common	Constipation
	Uncommon	Xerostomia, glossitis
	Rare	Intestinal hypomotility (ileus)
	Not known	Acute pancreatitis
Hepatobiliary disorders	Uncommon	Bile duct dyskinesia
	Not known	Sphincter of Oddi dysfunction
Skin and subcutaneous tissue disorders	Common	Transient rash, sweating
	Uncommon	Pruritus, urticaria, other rash and in very uncommon cases bleeding urticaria
Renal and urinary disorders	Uncommon	Urinary retention, anti-diuretic effect
Reproductive system and breast disorders	Uncommon	Reduced potency, galactorrhoea, dysmenorrhoea and amenorrhoea
General disorders and administration site condition	Common	Fatigue, drowsiness
	Uncommon	Oedema of the lower extremities, asthenia, oedema, hypothermia
Investigations	Common	Weight increase

[1]Visual effects have been reported in infants and children exposed to methadone during pregnancy

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.

<u>Reporting of suspected adverse reactions</u>

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via Yellow Card Scheme Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

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. Toxic leukoencephalopathy has been observed with methadone overdose.

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 1 to 3 hours, 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

Pharmacotherapeutic group: Drug used in opioid dependence

ATC code: N07BC02

Mechanism of action

Methadone is a strong 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 receptors.

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 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 being 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

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 12-18 (mean 15) 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 13-47 hours (mean 25) hours reflecting only clearance.

Methadone and its metabolites are excreted to varying degree in the feces 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).

5.3 Preclinical safety data

In mice, methadone reduces estriol and FSH levels resulting in an increase in resorption sites and decrease in implantation sites, while methadone administration to male rats prior to mating results in adverse effects on their progeny, particularly decreased birth weights and increased neonatal mortality, due to decreased LH and testosterone levels. Methadone induces sexual dysfunction in both sexual performance and sexual motivation in hamsters.

Methadone at high doses caused birth abnormalities in marmots, hamsters and mice, in which most reports were of exencephaly and defects in the central nervous system. Rachischisis in the cervical region was found occasionally in mice. Non-closure of the neural tube was found in chicken embryos. Methadone was not teratogenic in rats and rabbits. Also a reduced number of young was found in rats and increased mortality, growth retardation, neurological behavioural effects and reduced brain weight were found in the pups. Reduced ossification of the digits, sternum and skull was found in mice and a smaller number of fetuses per litter. No carcinogenicity studies have been carried out.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sorbitol, liquid non-crystallising (E420)

Glycerol (E422)

Sodium benzoate (E211)

Citric acid monohydrate (E330)

Colour Brilliant blue FCF (E 133)

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 below 25°C in the original package to protect from light.

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

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

6.5 Nature and contents of container

Type III, brown glass bottle containing 100 ml concentrate for oral solution sealed with screw cap PP 28 with PE-liner or with screw cap PP 28 child-resistant tamper evident ring with embossing and PE-liner, and a package leaflet in a carton box.

Type III, brown glass bottle containing 1000 ml concentrate for oral solution sealed with screw cap PP 28 with PE-liner or with screw cap PP 28 child-resistant tamper evident ring with embossing and PE-liner, and a package leaflet in a carton box.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

The drug product is supplied in dispensing packs which are only to be used by healthcare professionals.

This product 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 MARKETING AUTHORISATION HOLDER

INN-FARM d.o.o.

Maleševa ulica 014

1000 Ljubljana

Slovenia

8 MARKETING AUTHORISATION NUMBER(S)

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13/05/2026