

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Metadon 2care4 5 mg tablets
Metadon 2care4 10 mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 5 mg tablet contains 5 mg of methadone hydrochloride.
Each 10 mg tablet contains 10 mg of methadone hydrochloride.

Excipient with known effect

Each 5 mg tablet contains 157 mg lactose monohydrate per tablet.
Each 10 mg tablet contains 71 mg lactose monohydrate per tablet.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablet

{Invented name} 5 mg tablets are white to almost white, round and flat 8 mm diameter tablets with the marking '5' on one side and score line on the other side.
The tablet can be divided into equal doses.

{Invented name} 10 mg tablets are white to almost white, round and flat 6 mm diameter tablets with the marking '10' on one side and score line on the other side.
The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Symptomatic maintenance treatment of opioid-dependent patients in parallel with medical and psychological treatment and social rehabilitation. Symptomatic treatment of severe chronic pain, which can be adequately managed only with opioid analgesics.

{Invented name} is indicated in adults.

4.2 Posology and method of administration

Posology

Pain conditions

The dosage should be adjusted and evaluated based on the effect for the individual patient.

The following dosage recommendations should only be considered as suggested approaches when treatment with {Invented name} is initiated and must be adjusted to the individual need for pain relief. In order to more rapidly achieve a full analgesic effect {Invented name} may initially be dosed with shorter dosage interval during a limited period.

Dose in opioid naive patient

When oral methadone is used in patients who have not already been treated with opioids, the usual initial dose is 5 mg 1-3 times/day. This is followed by slow titration to effect. The titration should continue during several weeks. The initial dose should be carefully evaluated before increase of the

dose is started.

Since the risk for very serious cardiac side effects are dose dependent the daily dose of methadone should in the usual case not exceed 100 mg/day. Treatment with higher doses should be restricted to physicians with extensive experience in methadone treatment.

More frequent administration may be necessary during initiation of methadone treatment in order to maintain adequate analgesic effect. Extreme caution is necessary at such administration to evaluate the effect of the treatment and to avoid overdosing, taking into account the long elimination half-life of methadone.

There is an increased risk of serious undesirable effects at repeated dosage especially for opioid naive patients.

Dose in non-opioid naive patient

Initial dose: 5-20 mg 2-3 times/day. Thereafter slow titration in steps of 5 mg to a maximum daily dose of 100 mg. If required the 5 mg tablet may be replaced or combined with {Invented name} 20 mg tablet.

Since the risk for very serious cardiac side effects are dose dependent the daily dose of methadone should in the usual case not exceed 100 mg/day. Treatment with higher doses should be restricted to physicians with extensive experience in methadone treatment.

More frequent administration may be necessary during initiation of methadone treatment in order to maintain adequate analgesic effect. Extreme caution is necessary at such administration to evaluate the effect of the treatment and to avoid overdosing, taking into account the long elimination half-life of methadone.

Elderly

Treatment in elderly should be performed with caution and with a reduced dose initially.

Paediatric population

{Invented name} is not recommended in children due to lack of clinical data to provide a suitable dosage regimen.

Other conditions

Patients with hypothyroidism, myxoedema, urethral stricture, asthma or decreased lung volume or prostate hypertrophy must receive a lower initial dose.

Hepatic impairment

Caution is advised if {Invented name} must be used in patients with hepatic impairment. In patients with liver cirrhosis the metabolism is delayed and the first-passage-effect is decreased. This may result in higher plasma levels of methadone. {Invented name} should be administered in a lower dose than the recommended and the clinical response of the patient should be used as guidance for further dosage.

Renal impairment

Caution is advised if methadone is used in patients with renal impairment. The dosage interval should be extended to at least 32 hours if GFR is 10-50 ml/min and to at least 36 hours if GFR is lower than 10 ml/min if methadone is taken once daily for substitution/maintenance treatment of withdrawal symptoms. A lower initial dose of methadone is recommended depending on the clinical response and degree of renal impairment in combination with a slower dose titration.

The dosage interval should be extended to at least 8 hours if the glomerular filtration rate (GFR) is 10-50 ml/min and to at least 12 hours if GFR is lower than 10 ml/min if methadone is taken several times daily against pain. A lower initial dose of methadone is recommended depending on the clinical response and degree of renal impairment in combination with a slower dose titration.

Maintenance treatment of opioid dependence

The usual initial dose is 10 - 30 mg. In patients with high opioid tolerance the initial dose is 25-40 mg. The dose is increased in steps of 10 mg at a time over a period of 3 weeks, usually to 70 or 80 mg. After a recommended stabilization period of 4 weeks, the dose is adjusted, until the patient has no intoxication dependence and does not show clinical signs of psychomotor function effects or abstinence symptoms. Usual dose is 60-120 mg methadone daily but some patients may need higher doses. {Invented name} 20 mg and 40 mg tablets are also available. The dosage should be determined based upon clinical assessment and supported by follow up of the serum levels. The recommended 24-hours level in serum at steady state is 600-1200 nmol (200-400 ng/ml). The clinical assessment is of great importance. Methadone is normally administered once daily. At a more frequent administration there is a risk of accumulation and overdose. Doses over 150 mg/day is very uncommon and should as far as possible be avoided due to an increased risk of QT-prolongation, torsade de pointes and cases of cardiac arrest.

The patient should be observed in connection to dosage increases so that unintended reactions can be discovered. The serum level of the patient is increasing during up to 2 hours and it is important that signs of overdose or other serious/unpleasant reactions are discovered.

The pharmacokinetics of methadone undergo adaptive changes during repeated administration of the drug. These changes have been attributed to an increase in clearance. In such cases the dose should be increased once or several times in order to maintain the optimal effect.

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

Elderly

Caution must be exercised after administration to elderly patients.

Paediatric population

{Invented name} is not recommended in children due to lack of clinical data to provide a suitable dosage regimen.

Other conditions

Patients with hypothyroidism, myxoedema, urethral stricture, asthma or decreased lung volume or prostate hypertrophy must receive a lower initial dose.

Hepatic impairment

Chronic viral hepatitis is common in addicts. Caution is advised if {Invented name} must be used in patients with hepatic impairment. In patients with liver cirrhosis the metabolism is delayed and the first- passage-effect is decreased. This may result in higher plasma levels of methadone. {Invented name} should be administered in a lower dose than the recommended and the clinical response of the patient should be used as guidance for further dosage.

Renal impairment

Caution is advised if methadone is used in patients with renal impairment. The dosage interval should be extended to at least 32 hours if GFR is 10-50 ml/min and to at least 36 hours if GFR is lower than 10 ml/min.

The treatment should be discontinued if the effect is not sufficient or if the patient does not tolerate the treatment. The effect must be evaluated in accordance with national guidance.

If the treatment must be discontinued this should be done by a gradual dose reduction. The dose can be reduced relatively fast in the beginning, but the reduction must be slow in the end phase (from 20 mg daily and downwards).

Method of administration

This product is for oral use only, and must not be injected.

Treatment goals and discontinuation

Before initiating treatment with Metadon 2care4, a treatment strategy including treatment duration and treatment goals should be agreed together with the patient in accordance with pain management guidelines. During treatment, there should be frequent contact between the physician and the patient to evaluate the need for continued treatment, consider discontinuation and to adjust dosages if needed. When a patient no longer requires therapy with methadone, it may be advisable to taper the dose gradually to prevent symptoms of withdrawal (see section 4.4). In absence of adequate pain control, the possibility of hyperalgesia, tolerance and progression of underlying disease should be considered (see section 4.4).

For further information, see national guidance for methadone treatment.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Respiratory depression.

Acute obstructive airway disease.

Concurrent administration of MAO-inhibitors or administration within two weeks after terminated treatment with MAO-inhibitors.

4.4 Special warnings and precautions for use

Cases of QT-interval prolongation and torsade de pointes have been reported during treatment with methadone, especially at high doses (>100 mg/day). Methadone should be administered with caution to patients at risk to develop prolonged QT-interval, e.g., in case of:

- known QT-prolongation in the anamnesis,
- advanced cardiac disease,
- concurrent treatment with medicinal products that potentially cause QT-prolongation,
- concurrent treatment with CYP3A4-inhibitors,
- ischemic cardiac disease and liver disease,
- electrolyte disorders (hypokalaemia or hypomagnesaemia).

EKG should be monitored in all patients before initiation of analgesic therapy as well as at steady state if other concurrent risk factors for QT-prolongation exist and in elderly patients when dosing of methadone exceeds 50 mg/day. EKG should also be monitored in all patients before initiation of therapy and at steady state before dose increase of methadone exceeding 100 mg/day.

Opioid Use Disorder (abuse and dependence)

Careful monitoring of patients is recommended, especially during the initiation and early stages of treatment when patients may develop signs of drug dependence and/or drug abuse. Regular consultations should be considered during the early stages of treatment to ensure good patient compliance and for assessment for potential drug dependence/abuse among high risk patients. Lower starting doses should be used in patients with a history of substance abuse with regular monitoring to ensure good patient compliance before increasing dose.

As with other opioids, tolerance, physical, and/or psychological dependence may develop upon repeated administration of methadone.

When used for the treatment of pain, repeated use of Metadon 2care4 can lead to Opioid Use Disorder (OUD). A higher dose and longer duration of opioid treatment can increase the risk of developing OUD.

Before initiating treatment with Metadon 2care4 and during the treatment, treatment goals and a

discontinuation plan should be agreed with the patient (see section 4.2). Before and during treatment the patient should also be informed about the risks and signs of OUD. If these signs occur, patients should be advised to contact their physician.

Abuse or intentional misuse of Metadon 2care4 may result in overdose and/or death.

The risk of developing Opioid Use Disorder 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.

Special precautions for use of methadone are the same as for opiates in general.

Hyperalgesia

As with other opioids, in case of insufficient pain control in response to an increased dose of methadone, the possibility of opioid-induced hyperalgesia should be considered. A dose reduction or treatment review may be indicated.

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.

Acute asthma attacks, severe obstructive pulmonary disease, cor pulmonale, impaired respiratory reserve, hypoxia and hypercapnia are relative contraindications. Each case must be assessed individually.

Concurrent administration of other opiates, alcohol, barbiturates, benzodiazepines and other strong sedative psychoactive drugs may potentiate the effect and the undesirable effects of methadone and should be avoided.

Concurrent treatment with narcotic antagonists or mixed agonists/antagonists should be avoided (with exemption for treatment of overdose) since this may cause withdrawal symptoms in physical addicted patients.

At the beginning of the dose increase period the patient must be monitored after the administration to observe potential abnormal reactions or undesirable effects. The patient has increased serum levels during up to 2 hours and it is important that possible overdose reactions or other dangerous/serious reactions are observed.

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.

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.

Methadone should be used with caution at impaired renal- or hepatic function. The metabolism of methadone may be reduced at impaired hepatic function and dose adjustment may be required (see section 4.2). A lower initial dose must be administered in patients with hypothyroidism, myxoedema (the medicinal product may increase the risk of respiratory depression and long-term CNS depression),

renal impairment (increased risk of seizures), hepatic impairment (opioids are metabolized in the liver), asthma or decreased lung volume (the medicinal product may suppress the respiratory reflex and increase the airway resistance), urethral stricture or prostatic hypertrophy (the medicinal product may cause urine retention) (see section 4.2).

Great caution must be exercised in case of potential head injury or at conditions involving increased intracranial pressure. Methadone should not be used in patients with intestinal pseudo-obstruction, acute abdomen and inflammatory bowel disease.

In patients with kidney stones or gallstones it may be necessary, in prevention, to give atropine or another spasmolytic.

Elderly patients and patients with cardiovascular diseases are at increased risk of hypotension and syncope.

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.

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).

Paediatric population

Children are more sensitive than adults, which is the reason why poisoning may occur at very low doses. To avoid that children by mistake take methadone when it is used at home, it should be stored in a safe place, kept out of reach of children.

This product contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Pharmacokinetic interactions

P-glycoprotein inhibitors: Methadone is a substrate for P-glycoprotein; all medicinal products which inhibit P-glycoprotein (e.g., quinidine, verapamil, ciclosporin) may therefore increase the serum concentration of methadone. The pharmacodynamic effect of methadone may also increase as a consequence of an increased passage through the blood-brain barrier.

CYP3A4-inducers: Methadone is a substrate for CYP3A4 (see section 5.2). Induction of CYP3A4 increases the elimination of methadone and leads to decreased plasma levels. Inducers of this enzyme (barbiturates, carbamazepine, phenytoin, nevirapine, rifampicin, efavirenz, amprenavir, spironolactone, dexamethasone. *Hypericum perforatum* (St John's wort)) may induce the hepatic metabolism. For example, after three weeks treatment with 600 mg efavirenz daily, the mean maximal plasma concentration and AUC were decreased with 48 % and 57 % respectively, in patients treated with methadone (35-100 mg daily).

The consequences of the enzyme induction are more pronounced if the inducer is administered after the treatment with methadone has been initiated. Abstinence symptoms have been reported as a consequence of such interactions and it may therefore be necessary to increase the methadone dose. If the treatment with a CYP3A4 inducer is terminated the methadone dose should be reduced.

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.

CYP3A4-inhibitors: Methadone is a substrate for CYP3A4 (see section 5.2). Inhibition of CYP3A4 decreases the elimination of methadone. Concurrent administration of CYP3A4-inhibitor (e.g., cannabinoids, clarithromycin, delavirdine, erythromycin, fluconazole, fluvoxamine, grapefruit juice, itraconazole, ketoconazole, fluvoxamine, cimetidine, nefazodone and telitromycine) may increase plasma concentrations of methadone. If these medicinal products are prescribed to patients on methadone maintenance treatment, one must be aware of the risk of overdose.

Fluoxetine increases the concentrations of the R-methadone by inhibition of CYP2D6.

Medicinal products which affect the acidity of the urine: Methadone is a weak base. Substances that acidify the urine (such as ammonium chloride and ascorbic acid) may increase the renal clearance of methadone. Patients treated with methadone should be recommended to avoid products containing ammonium chloride (sal ammoniac).

Concurrent treatment of HIV-infection: Some protease inhibitors (amprenavir, nelfinavir, lopinavir/ritonavir and ritonavir/saquinavir) seem to lower the serum levels of methadone. Plasma levels of zidovudine (a nucleoside analogue) increase with methadone use, after both peroral and intravenous administration of zidovudine. This is more pronounced when zidovudine is given peroral than after intravenous administration. These observations are most probably caused by an inhibition of zidovudine glucoronidation and by the thereby decreased elimination of zidovudine. During methadone treatment the patients must be carefully monitored for signs of toxic effects of zidovudine, which possibly may require a decrease of the zidovudine dose.

Didanosine and stavudine: Methadone delays the absorption and increases the first pass metabolism of stavudine and didanosine, which leads to a decreased bioavailability of stavudine and didanosine.

Methadone may double the serum levels of desipramine, a CYP2D6 substrate. Inhibition of CYP2D6 may lead to increased plasma concentration of concurrent administered medicinal products metabolised by this enzyme. These include some tricyclic antidepressants (e.g., clomipramine, nortriptyline and desipramine), phenothiazine-neuroleptics (e.g., perphenazine and thioridazine), risperidone, atomoxetine, some Type 1c-antiarrhythmics (e.g. propafenone and flecainide) as well as metoprolol. Tamoxifen is a pro-drug which requires metabolic activation by CYP2D6. Tamoxifen has an important active metabolite, endoxifen, which is produced by CYP2D6 and which contributes significantly to the effect of tamoxifen. Inhibition of CYP2D6 by methadone may lead to decreased plasma levels of endoxifen.

Pharmacodynamic interactions

Opioid antagonists: Naloxone and naltrexone counteracts the effect of methadone and induce abstinence.

CNS-depressive products: Medicinal products with a sedative effect on the central nervous system may give an 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. At methadone treatment, the slowly eliminated substance methadone, gives rise to a slow tolerance development and each 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 during careful observation.

The concomitant use of opioids and gabapentinoids (gabapentin and pregabalin) increases the risk of opioid overdose, respiratory depression, and death.

Antimotility products: Concurrent use of methadone and antimotility products (loperamide and diphenoxylate) may result in severe constipation and increase the CNS depressant effects. Opioid analgesic may in combination with antimuscarinic products give severe constipation or paralytic ileus, especially at long-term use.

QT-prolongation: Methadone should not be combined with medicinal products which may prolong the QT-interval, such as antiarrhythmics (sotalol, amiodarone, flecainide), antipsychotics (thioridazine, haloperidol, sertindole, phenotiazines), antidepressants (paroxetine, sertraline) or antibiotics (erythromycine, clarithromycine).

MAO-inhibitors: Concurrent administration of MAO-inhibitors may result in reinforced CNS-inhibition, severe hypotension and/or apnoea. Methadone should not be given in combination with MAO-inhibitors or within two weeks after such administration (see section 4.3).

Cannabidiol: Concomitant administration of cannabidiol may result in increased plasma concentrations of methadone.

Opioid analgesics delay gastric emptying, so that some test results become invalid. The passage of technetium Tc 99m-disofenin to the small intestine may be prevented and the activity of plasma amylase and plasma lipase may be increased because opioid analgesics may cause constriction of sphincter of Oddi and increased biliary tract pressure; these effects lead to a delayed visualization and thereby resembles an obstruction of the bile duct. The diagnostic value of the determination of these enzymes may be deteriorated up to 24 hours after administration of the medicinal product. The pressure in the cerebrospinal fluid (CSF) may be increased; the effect is secondary to respiratory depression - induced carbon dioxide retention.

4.6 Fertility, pregnancy and lactation

Pregnancy

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.

Withdrawal symptom/respiratory depression may occur in neonates of mothers that were treated with methadone chronically during the pregnancy. A QT prolonging effect following maternal methadone exposure cannot be excluded, and a 12-lead electrocardiogram should be performed if the neonate has bradycardia, tachycardia or an irregular heart rate. Animal studies have shown reproductive toxic effects (see section 5.3). In general, it is recommended not to detoxify the patient, especially not after the 20th week of pregnancy, instead maintenance treatment with methadone is recommended. Use of methadone immediately before and after delivery is not recommended due to the risk of neonatal respiratory depression.

Breastfeeding

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 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.

4.7 Effects on ability to drive and use machines

Methadone affects the psychomotoric functions until the patient has been stabilized on a suitable level. The patient should therefore not drive or use machines until the stabilization has been achieved and no misuse symptoms have occurred during the last six months. How soon the patient is able to drive or use machines varies to a high extent from individual to individual and must be determined by the physician. For further information reference is made to national guidelines for methadone treatment.

4.8 Undesirable effects

The undesirable effects of methadone treatment are mainly the same as at with treatment with other opioids. The most common undesirable effects are nausea and vomiting that are observed in approximately 20 % of the patients.

The most serious undesirable effect is respiratory depression, which may occur in the stabilization phase. Apnea, shock and cardiac arrest have occurred.

The undesirable effects are presented within each frequency after decreasing seriousness with use of the following categories: very common ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1\,000$ to $< 1/100$), rare ($\geq 1/10\,000$ to $< 1/1\,000$); very rare ($< 1/10\,000$), not known (cannot be estimated from the available data).

System organ Class	Very common ($\geq 1/10$)	Common ($\geq 1/100$ to $< 1/10$)	Uncommon ($\geq 1/1\,000$ to $< 1/100$)	Rare ($\geq 1/10\,000$ to $< 1/1\,000$)	Not known (cannot be estimated from the available data)
Blood and lymphatic system disorders					reversible thrombocytopenia has been reported in opioid patients with chronic hepatitis
Metabolism and nutrition disorders		fluid retention	anorexia		hypokalaemia, hypomagnesaemia, hypoglycaemia
Psychiatric disorders		euphoria, hallucinations	dysphoria, agitation, insomnia, disorientation, impaired libido		Dependence, mood change
Nervous system disorders:		sedation	headache, syncope		
Eye disorders		blurred vision, miosis			
Ear and labyrinth disorders		vertigo			

Cardiac disorders				bradycardia, palpitations, cases of prolonged QT-interval and torsades de pointes have been reported at treatment with methadone, especially at higher doses	Cardiac arrest, ventricular arrhythmia, ventricular fibrillation, ventricular tachycardia
Vascular disorders:			facial flush, hypotension		postural hypotension
Respiratory, thoracic and mediastinal disorders			pulmonary oedema, respiratory depression		Central sleep apnoea syndrome
Gastrointestinal disorders	nausea, vomiting	constipation	dryness of the mouth, glossitis		Acute pancreatitis
Hepatobiliary disorders			bile duct, dyskinesia		Sphincter of Oddi dysfunction
Skin and subcutaneous tissue disorders		transient rash, sweating	pruritus, urticaria, other rash and in very rare cases bleeding urticaria.		
Renal and urinary disorders			urine retention and antidiuretic effect		
Reproductive system and breast disorders			impaired potency and amenorrhea		
General disorders and administration site conditions		fatigue	oedema in the lower limbs, asthenia, oedema		Sudden death, hypothermia
Investigations		Weight increase			

Reporting of suspected adverse reactions

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 the national reporting system listed in [Appendix V](#)**.

4.9 Overdose

Symptoms

Severe overdosage is characterized by respiratory depression, extreme drowsiness progressing to stupor or coma, maximum pupillary constriction, slackness in the skeletal muscle, cool and moist skin and sometimes bradycardia and hypotension. Apnea, cardiovascular failure, cardiac arrest and death may occur in serious cases of overdosage. Hypoglycaemia has been reported.

Toxic leukoencephalopathy has been observed with methadone overdose.

Management

Secure the airways through assisted or controlled ventilation.

It may be necessary to use opioid antagonists, but since the effect duration for methadone is long (36-48 hours) and the duration for the mostly used antagonist, naloxone, is only 1-3 hours, the antagonist treatment must be repeated if required. Antagonists must not be given unless signs of respiratory failure or unconsciousness exist. If the patient is physically dependent on narcotics the administration of an antagonist may lead to acute withdrawal symptoms. If possible, the use of antagonists should be avoided in such patients, but if it is shown that it is necessary to administer antagonists due to severe respiratory depression, great caution must be taken and the antagonist dose must be low if methadone poisoning is suspected.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Drugs used in opioid dependence, ATC code: N07BC02

Methadone is an opioid which belongs to the same group as morphine. The substance has an agonist effect on the opioid receptors in the brain, bone marrow and the nervous system, with high affinity for μ -receptors as well as some affinity for σ - and κ -receptors. Methadone acts in a similar way as morphine, but has a less sedative effect. The use of methadone may reduce or eliminate the effects of other opioids. Methadone may when carefully titrated be given orally, without giving any euphoria but only a condition of "normality" during 24-32 hours, followed by increasing withdrawal symptoms, unless a new dose is administered.

5.2 Pharmacokinetic properties

Absorption

The bioavailability is above 80 %. Steady state concentrations are reached within 5-7 days.

Distribution

The distribution volume is 5 L/kg. Methadone is mainly bounded to acid α -1-glycoprotein, but also to albumin and other plasma- and tissue proteins. The plasma: whole blood quote is approximately 1:3. Methadone is distributed in the tissues, with higher concentrations in liver, lungs and kidneys than in the blood.

Biotransformation

Mainly catalysed by CYP3A4, but CYP2D6 and CYP2B6 also participate, but to a smaller extent. The metabolism mainly consists of N-demethylation, which gives 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 methanol followed by N-

demethylation to normetadole also exists to a certain extent. Other metabolic reactions also occur and at least eight other metabolites are known.

Elimination

Elimination half-life: single dose 10-25 hours. Repeated doses: 13-55 hours. Plasma clearance is about 2 ml/min/kg. Approximately 20-60 % of the dose is eliminated in the urine in 96 hours (approx. 33 % in unmodified form, approx. 43 % as EDDP and approx. 5-10 % as EMDP). The elimination of unmodified methadone in the urine is pH-dependent and increases with increasing acidity of the urine. Approximately 30 % of the dose is eliminated in faeces, but this part is normally decreased at higher doses. Approximately 75 % of the eliminated substance is in unconjugated form.

Special patient population

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

Due to increased exposure, caution is advised in the treatment of patients with renal or hepatic impairment (see sections 4.2 and 4.4).

5.3 Preclinical safety data

Methadone at high doses caused malformations in marmots, hamsters and mice, in which most of the reports dealing with exencephaly and defects in the central nervous system. Rachischisis in the cervical region was seen occasionally in mice. Lack of closure of the neural tube was found in chicken embryos. Methadone was not teratogenic in rats and rabbits. Further a reduced number of babies were observed in rats and increased mortality, growth retardation, neurological behavioral effects and reduced brain weight were found in the children. Reduced ossification of the fingers/toes, sternum and skull were found in mice and the number of fetus per litter decreased. No carcinogenicity studies have been performed.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate
Pregelatinised maize starch
Magnesium stearate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

5 years.

6.4 Special precautions for storage

Do not store above 30°C.

6.5 Nature and contents of container

Al/PVC/PVDC blisters or white HDPE bottles with PP Random Copolymer child-resistant closure.

Pack-sizes:

10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95 and 100 tablets in blisters.

25, 100 and 200 tablets in bottles.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

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

7. MARKETING AUTHORISATION HOLDER

[To be completed nationally]

8. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

[To be completed nationally]

10. DATE OF REVISION OF THE TEXT

20 April 2026