SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Metadon Pharmadone 10 mg oral solution
Metadon Pharmadone 15 mg oral solution
Metadon Pharmadone 20 mg oral solution
Metadon Pharmadone 25 mg oral solution
Metadon Pharmadone 30 mg oral solution
Metadon Pharmadone 35 mg oral solution
Metadon Pharmadone 40 mg oral solution
Metadon Pharmadone 45 mg oral solution
Metadon Pharmadone 50 mg oral solution
Metadon Pharmadone 55 mg oral solution
Metadon Pharmadone 60 mg oral solution
Metadon Pharmadone 70 mg oral solution
Metadon Pharmadone 80 mg oral solution
Metadon Pharmadone 90 mg oral solution
Metadon Pharmadone 100 mg oral solution
Metadon Pharmadone 110 mg oral solution
Metadon Pharmadone 120 mg oral solution
Metadon Pharmadone 130 mg oral solution
Metadon Pharmadone 140 mg oral solution
Metadon Pharmadone 150 mg oral lösning

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each dose (50 ml) oral solution contain 10 mg, 15 mg, 20 mg, 25 mg, 30 mg, 35 mg, 40 mg, 45 mg, 50 mg, 55 mg, 60 mg, 70 mg, 80 mg, 90 mg, 100 mg, 110 mg, 120 mg, 130 mg, 140 mg or 150 mg methadone hydrochloride.

Excipient(s) with known effect: glucose, sucrose (11 g/dose), methylparahydroxibensoate.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Oral slution.
Clear colourless solution with smell and taste of raspberry.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Substitution therapy for the treatment of opioid addiction.
Treatment with methadone is one part of a broader treatment programme including medical, social and psychological care. All treatment with methadone is based on current guidelines from national authorities.

4.2 Posology and method of administration

Posology
The dosage is individual from patient to patient. The usual initial dose is 10-30 mg. For patients with high opioid tolerance, the initial dose is 25-40 mg.
Recommended increase of the dosage to maintenance level should be in steps of at maximum 10 mg at a time over a period of 3 weeks, usually to 70 or 80 mg. After a recommended stabilisation 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.
The majority of patients within methadone substitution therapy need 60-120 mg per day to achieve a safe and efficient treatment however; some individuals may require higher doses.

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/l (200-400 ng/ml). The clinical assessment is of great importance.
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. The reason for this dose limitation is an increased frequency of QT-prolongation, Torsade's de Pointes and cases of cardiac arrest within higher dose ranges (see section 4.4). High doses may also elicit low-grade (but unwanted) euphoria during a couple of hours after the daily dose.

The patient should be observed in relation to dose increases to discover unwanted reactions. The patient obtains an increased serum level for up to two hours, and it is important that signs of overdose or other serious/unpleasant reactions are discovered.

Some patients develop auto-induction, witch leads to the medication being more rapidly metabolised in the body. In such cases, the dose must be increased once or more to maintain optimal effect.

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

If treatment is to be ended the dose should be reduced gradually. 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).

Elderly
Caution must be exercised after administration to elderly and ill patients.

Paediatric population
Methadone must not be given to children (see section 4.3).

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 hepatic impairment is frequent for drug addicts injecting narcotics. Caution should be exercised if this product is used in patients with liver impairment. In patients with liver cirrhosis the metabolic breakdown is delayed and the first-pass effect is reduced. This may result in higher

methadone plasma levels. Metadon Pharmadone should be administered at a dose lower than that usually recommended and the patients response should be used as a guideline for further dosage requirements.

Renal impairment:
Caution should be exercised in the use of methadone in patients with renal impairment. The dose interwal 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 10ml/min.

Method of administration

For oral administration only. This product is to be used undiluted.
Further references are given in national guidelines for methadone treatment.

4.3 Contraindications

- **Respiratory depression if severe**
- Hypersensitivity to methadone hydrchloride or any of the excipients listed in section 6.1.
- Treatment with narcotic antagonists or agonists/antagonists (with exceptions for treatment of over dosage of such substances)
- Concurrent administration with MAO inhibitors or within 2 week of discontinuation of treatment with them.
- Children
- Acute obstructive airway disease

4.4 Special warnings and precautions for use

Special precautions for use of methadone are the same as for opiates in general.
Acute asthma attack, chronical obstructive airways disease, cor pulmonae, decreased respiratorical reserve, hypoxia and hypercapnia are conditional contraindications and must be evaluated from case to case, Section 4.3.

In cases of impaired hepatic and renal function, methadone must be used with caution. The metabolism of methadone may be reduced in cases of impaired hepatic function, and dose adjustment may be necessary (see 4.2). A lower initial dose must be administered to patients with hypothyroidism, myxedema, (it can increase the risk of respiratory depression and prolonged CNS depression), renal (increased risk of convulsions) and hepatic impairment (opioids metabolised in liver), asthma or decreased lung volume (it may decrease respiratory drive and increase airway resistance) urethral stricture or prostatic hypertrophy (it may cause urinary retention) (see 4.2).

Prophylactic treatment with administration of atropine or other spasmolytics may be necessary for patients with renal calculus or gallstones.

Concurrent administration of other opiates, alcohol, barbiturates, benzodiazepines or other psychoactive drugs with strong sedative effect may increase the effect and the side reactions of methadone and should be avoided.

The patient obtains an increased serum level for up to two hours, and it is important that signs of overdose or other serious/unpleasant reactions are discovered. During the period of dose titration observation of the patient should be considered in purpouse to discover unwanted reactions.

Methadone should not be used by patients with paralytic ileus, intestinal pseudo-obstruction and acute abdomen- and inflammatory bowel disease and caution should be exercised in case of head injury,

raised itracranial pressure.

Cases of QT-interval prolongation and torsade de points have been reported during treatment with methadone, particularly at high doses (» 100mg/d). 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 heart disease or ischemic heart disease, known history of QT prolongation, family history of sudden death, electrolyte abnormalities (hypokalaemia, hypomagnesaemia), concomitant treatment that have a potential for QT prolongation, concomitant treatment with drugs witch may cause electrolyte abnormalities, concomitant treatment with cytochrome P450CYP 3A4 inhibitors (see section 4.5).
In patients with recognised risk factors for QT prolongation, especially women, ECG monitoring is recommended.

At the beginning of the dose increase period the patient must be observed after administration to record any abnormal/adverse reactions. The patient will have increased serum levels for up to two hours, and it is important that any overdose reactions or other dangerous/severe reactions can be recorded.

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

Metadon Pharmadone contains methylparahydroxybesoate witch may, cause allergic reactions.
This product contains also 11g sucrose and 2,5g glucose per dose. Patients with diabetes mellitus should take precaution.

Paediatric population
Children are more sensitive than adults, that is why poisoning may occur at very low doses. To avoid unintentional intake of methadone by children, methadone should in cases when it is taken home, be kept in a safe place where children cannot reach it.

4.5 Interaction with other medicinal products and other forms of interaction

Pharmacokinetic interactions:

P-glycoprotein inhibitors: Methadone is a substrate of p-gycoprotein: allmedicinal products that inhibit p-glycoprotein (e.g. qunidine, verapramil, ciklosporin), may therefore raise the serum concentration of methadone. the pharmacodynamic effect of methadone may also increase due to 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, rifampicine, 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 methadone dose. If treatment with a CYP3A4 inducer is interrupted, the methadone dose should be reduced.

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. fluconazole, grapefruit juice, itraconazole, ketoconazole, 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 bas 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.

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

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, 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.

Didanosine and stavudine: Methadone delays the adsorption and increases the first pass metabolism of stavudine and didanosine witch results in a decreased bioavailability of stavudine and didanosine.

Methadone may double the serum levels of desipramine, a CYP2D6 substrate. Inhibition of CYP2D6 may cause increased plasma concentrations of concomitantly administered medicinal products that are metabolised by CYP2D6. These products include, but are not limited to, TCA (e.g. clomipramine, nortriptyline, desipramine), phentiazine neuroleptics, (e.g., perfenazine and thioridazine), risperidone, atomoxetine, certain Type I antiarrhythmics (e.g. propafenone and flecainid) and metoprolol. Tamoxifen is a pro-drug that requires metabolic activation by CYP2D6. Tamoxifen has an active metabolite, endoxifen that is formed by CYP2D6 with a significant contribution to the effect. Inhibition of CYP2D6 by methadone may lead to reduced plasma concentrations of endoxifen.

Pharmacodynamic interactions:

Opioid antagonists: Naloxone and Naltrexone counteracts the effects of methadone and induces abstinence.

C'NS 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 l-2 week give rise to symptoms of respiratory depression. The dose adjustments must therefore be made with caution and the dose increased gradually with careful observation.

Peristalsis inhibition: Concomitant use of methadone and peristalsis inhibiting medicinal products (loperamide and diphenoxylate) may result in severe obstipation and increase the CNS depressant effect. 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 antiarrhythmics; (sotalol, amiodarone and flecainid), antipsychotics (thioridazine, haloperidol, sertindol and phenotiazines), antidepressants (paroxetine, sertraline) or antibiotics (erythromycin, clarithromycin).

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).

Opioid analgesics delay gastric emptying thereby invalidating test results. Delivery of technetium Tc 99m disofenin to the small bowel may be prevented and plasma amylase and plasma lipase activity may be increased 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. The diagnostic utility of determinations of these enzymes may be compromised for up to 24 hours after the medication has been given. Cerebrospinal fluid pressure (CSF) may be increased; effect is secondary to respiratory depression - induced carbon dioxide retention.

4.6 Fertility, pregnancy and lactation

Pregnancy:
Limited data on the use of methadone in pregnancy of humans show no elevated risk of congenital malformations. Withdrawal symptoms/respiratory depression might occur in neonates of mothers that were treated with methadone chronically during 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. Data from animal studies have shown reproduction toxicity (see section 5.3). It is generally advisable not to detoxify the patient, especially not after the 20th week of pregnancy, but to administer maintenance treatment with methadone. The use of Methadone Pharmadone oral solution just before and during birth is not recommended due to the risk of neonatal respiratory depression.

Lactation:
Methadone is excreted in breast milk and the average milk/plasma ratio is 0.8. Breast-feeding may be given on doses of up to 20mg per day. At higher doses the benefits of breast-feeding must be weighed against the possible adverse effects on the infant.

4.7 Effects on ability to drive and use machines

Methadone will affect the psychomotor functions until the patient has been stabilised at a suitable level. The patient should therefore not drive or use machines until stabilisation has been achieved and there have been no symptoms of abuse for the last six months. When driving and use of machines can be resumed, is largely dependent on the individual patient and must be determined by the physician. For further information see the national guidelines for methadone treatment.

4.8 Undesirable effects

The undesirable effects of methadone treatment are in general the same as when treated with other opioids. The most common side effects are 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.
The most serious side 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 side effects 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 (≥ 1/1000 to < 1/100), rare (≥ 1/10000 to < l/ 1000), very rare (<1/10000), 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 patients with chronic hepatitis
Metabolism and nutrition disorders	Not known Common Uncommon	hypokalemia, hypomagnesemia fluid retention anorexia
Psychiatric disorders	Common Uncommon	euphoria, hallucinations dysphoria, agitation, insomnia, disorientation, reduced libido
Nervous system disorders	Common Uncommon	sedation headache, sycope
Eye disorders	Common	blurred vision, miosis
Ear and labyrinth disorders	Common	vertigo
Cardiac disorders	Rare	bradycardia, palpitations, cases of prolonged QT intervals and “torsade de pointes” have been reported in treatment with methadone, especially with high doses
Vascular disorders	Uncommon	facial flush, hypotension
Respiratory, thoracic and mediastinal disorders	Uncommon	pulmonary oedema, respiratory depression
Gastrointestinal disorders	Very common Common Uncommon	nausea, vomiting obstipation xerostomia, glossitis
Hepatobiliary disorders	Uncommon	bile duct dyskinesia
Skin and subcutaneous tissue disorders	Common Uncommon	transient rash, sweating pruritus, urticarial, other rash and in very uncommon cases bleeding urticaria

Renal and urinary disorders	Uncommon	urinary retention and antidiuretic effect
Reproductive system and breast disorders	Uncommon	reduced potency and amenorrhea
General disorders and administration site conditions	Common Uncommon	fatigue oedema of the lower extremities, asthenia, oedema
Investigations	Common	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, obstipation and perspiration often remain.
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 lasing.

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
[To be completed nationally]

4.9 Overdose

Symptoms
Severe overdose is characterised by respiratory failure, extreme drowsiness that develops into stupor or coma, maximum pupillary constriction, skeletal-muscle flaccidity, cold and clammy skin and occasionally bradycardia and hypotension. Apnoea, cardiovascular failure, cardiac arrest and death may occur in serious cases of overdose, especially in intravenous administration. Cases of acute bilateral hearing loss have been reported following overdose of metadone.

Treatment
Treatment is supportive and use of an opioid antagonist such as naloxone, malorphine or levallorphan should be limited to those patients wth demonstrated repiratory or cardiovascular depression due to methadone.
Naloxone is the preferred antagonist as there is less likehood of further respiratory depression from the effects of the opioid antagonist. Use of an opioid antagonist may need to be continued for up to 48 hours due to the duration of action of methadone, and for this reason respiratory and cardiovascular monitoring is mandatory. Dialysis, CNS stimulation and respiratory stimulants are contraindicated. Acidification of the urine will increase the renal clearence of the drug.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Methadone is a narcotic analgesic that belongs to the same group as morphine. The substance has an agonist effect on the opiate receptors in the brain, bone marrow and nervous system, with high affinity

for the μ receptors, and also some affinity for the σ and κ receptors. Methadone acts in a similar way as morphine, but has a less sedative effect. The use of methadone can reduce or eliminate the effect of other opiates. Methadone, at a carefully titrated dose can be given orally, with no euphoria but simply a state of “straight” for 24-32 hours, followed by gradually increasing withdrawal symptoms, unless a new dose is applied.

5.2 Pharmacokinetic properties

Absorption:

Absorption: Methadone undergoes considerable first-passage metabolism.

Methadone is a basic and lipophilic substance which is almost completely absorbed from the gastrointestinal tract. Tmax ranges between 1.5 and 3 hours. Its bioavailability is over 80%. Steady-state concentrations are achieved within 5-7 days.

Distribution:

Approximately 89% of methadone is absorbed by the body and binds to proteins. Methadone binds primarily to alpha-l-glycoprotein in plasma. The binding of methadone to non vascular tissue proteins is strong and methadone accumulates in the liver, kidneys and other organs. Volume of distribution of methadone is approximately 5 L / kg.

Metabolism:

Catalysed primarly by CYP3A4, but CYP2D6 and CYP2B6 are also involved, but to a lesser extent. Metabolism is mainly N-demethylation, wich produces the most important metabolites 2-ethylidine,1,5-dimethyl-3,3-diphenylpyrrodiline (EDDP) and 2-ethyl-5-methyl-3,3-diphenyl-1-pyrrolidine (EMDP), which are both inactive. Hydroxylation to methanol succeded by N-demethylation to normethadol also occurs to to some extent. Other metabolic reactions also also occur and at least eight other metabolites are known.

Elimination:

Elimination: Elimination half-life: Values between 15-60 hours have been reported, but the inter-individual variations are considerable. In studies with chronic administration of methadone, a tendency towards shorter elimination half-lives have been observed, possibly due to auto-induction of the elimination. Plasma clearance is around 2 ml/min/kg. About 20-60 % of the dose is eliminated in urine over 96 hours (about 33 % in unmodified form, about 43 % as EDDP and about 5-10 % as EMDP). The ratio between EDDP and unmodified methadone is usually much higher in urine in patients receiving methadone treatment compared to normal overdoses. Elimination of unmodified methadone in urine is pH-dependent and increases with increasing acidity 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 clearence of methadone is decreased only to some extent in elderly (>65 years).

Because of increased exposure, caution is advised in the treatment of patients with renal and hepatic impirments (see sections 4.2 and 4.4).

5.3 Preclinical safety data

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. Neural tube defects 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. A reduced number of young was found in rats and inreased 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 foetuses per litter. No carcinogenicity studies have been carried out.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Glucose, Sucrose (11 g/dose), Methylparahydroxibensoate (E 218), Raspberry aroma, Water purified.

6.2 Incompatibilities

None known

6.3 Shelf life

3 years

6.4 Special precautions for storage

This medicine does not require any special storage conditions.

6.5 Nature and contents of container

Plastic bottle of polyethylene sealed with tamper evident, child-resistant screw cap of polyethylene. The bottle contains 50 ml oral solution.

Pack sizes: 1 bottle (all strengths) and 7 bottles (1x7) (50 mg, 60 mg, 70 mg, 80 mg, 90 mg, 100 mg, 110 mg, 120 mg, 130 mg, 140 mg and 150 mg).

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special 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

Date of first authorisation: 2008-12-05

10. DATE OF REVISION OF THE TEXT

18 November 2016