SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Metadon Abcur 20 mg tablets
Metadon Abcur 40 mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

20 mg: 1 tablet contains 20 mg methadone hydrochloride.
40 mg: 1 tablet contains 40 mg methadone hydrochloride.

Excipients with known effect:
20 mg: 1 tablet contains 90 mg lactose monohydrate.
40 mg: 1 tablet contains 180 mg lactose monohydrate.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablets
20 mg: White to off-white, round, flat bevelled tablet, concave with a score line on one side and embossing M20 on the other side, tablet dimension 7 x 3.2 mm.
40 mg: White to off-white hexagonal, with score line on one side and embossing M40 on the other side, tablet dimension 9.5 x 3.2 mm.

The tablet can be divided into equal doses.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of severe chronic pain, which can be adequately managed only with opioid analgesics.

4.2 Posology and method of administration

Posology

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 Metadon Abcur is initiated and must be adjusted to the individual need for pain relief. In order to more rapidly achieve a full analgesic effect Metadon Abcur 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 20 mg or 40 mg tablet may be replaced or combined with Metadon Abcur 5 mg or10 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
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
Caution is advised if Methadone Abcur 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. Metadon Abcur should be administrated 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.

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

Treatment goals and discontinuation
Before initiating treatment with Metadon Abcur, 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 tolerance and progression of underlying disease should be considered (see section 4.4).

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.
Contraindicated in children.

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 (hypokalemia or hypomagnesemia).

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)
As with other opioids, tolerance, physical, and/or psychological dependence may develop upon repeated administration of methadone.
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 doses starting doses should be used in patients with a history of substance abuse with regular monitoring to ensure good patient compliance before increasing dosse.

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

When used for the treatment of pain, repeated use of Metadon Abcur s 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 [product name] 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 Abcur 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.

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 pshycoactive drugs may potentiate the effect and the undesirable effects of methadone and should be avoided.

Risk from concomitant use of sedative medicines such as benzodiazepines or related drugs:
Concomitant use of Metadon Abcur tablets 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 Metadon Abcur tablets 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).

Concurrent treatment with narcotic antagonists or mixed agonists/antagonists should be avoided (with exemption for treatment of overdoseage) 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.

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 administrated 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).

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.

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 disease 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).

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

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.

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 administrated 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.

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, grapefruit juice, itraconazole, ketoconazole, fluvoxamine, cimetidine, nefazodone and telitromycine) may increase plasma concentrations of methadone. At concurrent fluvoxamine treatment a 40-100 % increase of the quote between the serum levels and the methadone dose has been shown. If these medicinal products are prescribed to patients on methadone maintenance treatment, one must be aware of the risk of overdose.

Fluoxetine increase 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. When ritonavir is administrated alone a 50% reduction of AUC for methadone has been shown. 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 och 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), phentiazine-neuroleptics (e.g. perphenazine and thioridazine), risperidone, atomoxetine, some Type 1c-antiarrhythmics (e.g. propafenone and flecainide) as well as metoprolole. Tamoxifen is a pro-drug which requires metabolic activation by CYPD6. 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
Opioide 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.

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).

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), antipsycotics (thioridazine, haloperidol, sertindole, phenothiazines), 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).

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 leads 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.

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

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

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.

4.6 Fertility, pregnancy and lactation

Pregnancy: Limited data on the use of methadone during pregnancy in humans show no increased risk of congenital malformation. 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). 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 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: In animal studies methadone induced a blockade in ovulation in female rats and dose-dependently blocked the sexual activity of male hamsters. Cases of male impotence have been reported amongst chronic methadone users.

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.

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 (≥ 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	**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)**	**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		hypokalemia, hypomagnesemia, hypoglycaemia
Psychiatric disorders		euphoria, hallucinations	dysphoria, agitation, insomnia, desorientation, impaired libido		dependece, mood chanege
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

System organ class	**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)**	**Not known (cannot be estimated from the available data)**
Gastrointestinal disorders	nausea, vomiting	constipation	dryness of the mouth, glossitis		
Hepatobiliary disorders			bile duct dyskinesia		
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
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.

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 as well as rare events of toxic leukoencephalopathy may occur in serious cases of overdosage. Hypoglycaemia has been reported.

Treatment: 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 administrate 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: Morphinelike analgetic, ATC code: N07BC02

Methadone is a narcotic analgesic which belongs to the same group as morphine. The substance has a 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 administrated.

5.2 Pharmacokinetic properties

Absorption Methadone is rapidly absorbed after oral administration, but undergoes considerable first-passage-metabolism. The bioavailability is above 80 %. Steady state concentrations are reached within 5-7 days.

Distribution The distribution volume is 5 L/kg. Protein binding: up to 90 % where the protein binding is higher for the inactive S-enantiomer, but with large individual variations. Methadone is mainly bounded to acid alfa-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 quote between EDDP and unmodified methadone is usually much higher in the urine of patients in methadone treatment than at normal overdoses. 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 young were observed in rats and increased mortality, growth retardation, neurological behavioral effects and reduced brain weight were found in the pups. Reduced ossification of the fingers/toes, sternum and skull were found in mice and the number of fetus per litter decreased. Genotoxicity studies yielded inconclusive results, indicating either the lack of a genotoxic potential or a weak positive effect. Carcinogenicity *s*tudies in mice and rats have detected no carcinogenic potential.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate
Maize starch
Talc
Povidone (PVP K-25)
Colloidal, anhydrous silica
Magnesium stearate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

20 mg: 5 years.
40 mg: 4 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

20 mg: HDPE-bottle with child-resistant HDPE-cap: 25, 100, 200 tablets.
PVC-PVDC/ALU blister: 10, 20, 30, 40, 50, 60, 70, 80, 90 and 100 tablets.

40 mg: HDPE-bottle with child-resistant HDPE-cap: 25 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

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

[To be completed nationally]

10. DATE OF REVISION OF THE TEXT

8-SEP-2023