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

Metadon 2care4 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.

Metadon 2care4 10 mg tablets are white to almost white, round and flat 6 mm 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.

Methadon 2care4 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 Metadone is initiated and must be adjusted to the individual need for pain relief. In order to more rapidly achieve a full analgesic effect Metadone 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 Metadon 2care4 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
Methadon 2care 4 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 Metadone 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. Metadone 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 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. Metadon 2care4 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 administrated once daily. At a more frequent administration there is a risk of accumulation and overdosage. 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 overdosage 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 buprenorfine/naloxene.

Elderly
Caution must be exercised after administration to elderly patients.

Paediatric population
Methadon 2care4 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 Metadone 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. Metadone 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.

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.

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 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.

Dependence/abuse
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 dose."

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

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 overdosage) 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).

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.

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, the Lapp 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 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, 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 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. 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), phentiazine-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 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.

<u>Pharmacodynamic interactions</u>

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.

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).

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.

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). 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 breast milk and the average milk/plasma quote is 0.8. Breast feeding may be performed at doses up to 20 mg daily. At higher doses the benefits of breast feeding must be weighed towards the possible negative effects of the child.

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 (≥ 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)	Very rare (< 1/10 000)	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, hypomagnesemia.
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 arrythmia, ventricular fibrillation, ventricular tachycardia
Vascular disorders:			facial flush, hypotension.			postural hypotension
Respiratory, thoracic and mediastinal disorders:			pulmonary oedema, respiratory depression.			
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, 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:

{to be completed nationally}

By reporting side effects you can help provided more information on the safety of this medicine.

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.

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 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: Drugs used in opioid dependence, ATC code: N07BC02

Methadone is a narcotic analgesic 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 administrated.

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 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 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

3 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

2care4 Generics ApS
Tømrervej 9
DK-6710 Esbjerg V
Denmark

8. MARKETING AUTHORISATION NUMBER(S)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT

13 September 2019