

## SUMMARY OF PRODUCT CHARACTERISTICS

### 1. NAME OF THE MEDICINAL PRODUCT

Metadon Abcur 5 mg tablets

### 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

5 mg: 1 tablet contains 5 mg methadone hydrochloride.

Excipients:

5 mg: 1 tablet contains 79.2 mg lactose.

For the full list of excipients, see section 6.1.

### 3. PHARMACEUTICAL FORM

Tablets

White to off-white, round, flat bevelled tablet, with score line on one side and embossing M5 on the other side.

The tablet can be divided into equal doses.

### 4. CLINICAL PARTICULARS

#### 4.1 Therapeutic indications

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

#### 4.2 Posology and method of administration

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 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 5 mg tablet may be replaced or combined with Metadon Abcur 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.

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

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. 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 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.

Some patients develop auto-induction, which leads to a faster metabolism of the medicinal product in the body. 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.

Caution must be exercised after administration to elderly patients. Methadone must not be given to children (see section 4.3). 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 Metadon 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 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).

For further information, see national guidance for methadone treatment.

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

### **4.3 Contraindications**

Respiratory depression.

Hypersensitivity to the active substance or to any of the excipients.

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.

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.

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.

Risk from concomitant use of sedative medicines such as benzodiazepines or related drugs:

Concomitant use of Metadon Abcur 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 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 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.

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.

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.

*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 ratio 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 administered alone a doubling 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 glucuronidation 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, give 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), antipsychotics (thioridazine, haloperidol, sertindole, phenothiazines), antidepressants (paroxetine, sertraline) or antibiotics (erythromycin, clarithromycin).

*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 the 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 20<sup>th</sup> 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.

*Lactation:* 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 ( $\geq 1/10$ ); 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 ( $< 1/10\ 000$ ).

##### **Investigations:**

*Common:* weight increase

##### **Metabolism and nutrition disorders:**

*Common:* fluid retention

*Uncommon:* anorexia

*Not known:* hypokalemia, hypomagnesemia

##### **Blood and lymphatic system disorders:**

*Not known:* reversible thrombocytopenia has been reported in opioid patients with chronic hepatitis.

##### **Respiratory, thoracic and mediastinal disorders:**

*Uncommon:* pulmonary oedema, respiratory depression

##### **Gastrointestinal disorders:**

*Very common:* nausea, vomiting

*Common:* constipation

*Uncommon:* dryness of the mouth, glossitis

##### **Psychiatric disorders:**

*Common:* euphoria, hallucinations

*Uncommon:* dysphoria, agitation, insomnia, desorientation, impaired libido

##### **Ear and labyrinth disorders:**

*Common:* vertigo

##### **Eye disorders:**

*Common:* blurred vision, miosis

##### **Nervous system disorders:**

*Common:* sedation

*Uncommon:* headache, syncope

**Skin and subcutaneous tissue disorders:**

*Common:* transient rash, sweating

*Uncommon:* pruritus, urticaria, other rash and in very rare cases bleeding urticaria

**General disorders and administration site conditions:**

*Common:* fatigue

*Uncommon:* oedema in the lower limbs, asthenia, oedema

**Vascular disorders:**

*Uncommon:* facial flush, hypotension

**Hepatobiliary disorders:**

*Uncommon:* bile duct dyskinesia

**Cardiac disorders:**

*Rare:* bradycardia, palpitations, cases of prolonged QT-interval and torsades de pointes have been reported at treatment with methadone, especially at higher doses.

**Renal and urinary disorders:**

*Uncommon:* urine retention and antidiuretic effect

**Reproductive system and breast disorders:**

*Uncommon:* impaired potency and amenorrhea

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 may occur in serious cases of overdosage.

*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  $\mu$ -receptors as well as some affinity for  $\sigma$ - and  $\kappa$ -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.

*Metabolism:* 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-ethylidene-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 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  
Maize starch  
Talc  
Povidone K25  
Colloidal, anhydrous silica  
Magnesium stearate

## **6.2 Incompatibilities**

Not applicable.

## **6.3 Shelf life**

5 years.

## **6.4 Special precautions for storage**

This medicinal product does not require any special storage conditions.

## **6.5 Nature and contents of container**

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

Not all pack sizes may be marketed.

## **6.6 Special precautions for disposal and other handling**

No special requirements.

## **7. MARKETING AUTHORISATION HOLDER**

Abcur AB  
Box 1452  
251 14 Helsingborg

## **8. MARKETING AUTHORISATION NUMBER(S)**

<To be completed nationally>

## **9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

2011-09-16

## **10. DATE OF REVISION OF THE TEXT**

2018-12-20