SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT
Methadon Molteni 5 mg/ml oral solution

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Methadon Molteni 5 mg/ml contains 5 mg of methadone hydrochloride in 1 ml. Excipient with known effect: Liquid maltitol.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM
Colourless to slightly yellow oral solution

4. CLINICAL PARTICULARS
4.1 Therapeutic indications
Treatment of abstinence symptoms of heroin /opiates aimed at detoxification.
Supplementary treatment of people dependent on opiates who are unable to stop using opiates.

4.2 Dosage and method of administration

Treatment of abstinence symptoms
Prescription of methadone must be above all carried out in specialized treatment centres due to the great risk the therapy brings.
In case it is not possible, a consultation at the nearest consultation centre for alcoholics and drug addicted is necessary.
Initial dose may be estimated according to the seriousness of abstinence symptoms. In the majority of cases the initial daily dose may be determined at 20 mg orally. After administration of the first dose (and after each increase of the dose) patient’s reaction should be monitored. In case of no decrease of abstinence symptoms, namely no decrease of pulse frequency, pupil dilation, increased peristaltics, another 20 mg dose of the product may be eventually administered orally after 3-4 hours.
The dose is increased by 10-20 mg per day until there are no signs of withdrawal or intoxication. Treatment usually continues with oral administration of methadone 30-50 mg per day and the dose may be in the course of few weeks gradually decreased.

Supplementary treatment
Note: see „Treatment of abstinence symptoms“. Initial dose may be determined as in case of addiction treatment. Daily dose (best in the form of an oral solution) is usually between 50-100 mg, mostly about 60 mg. Treatment usually lasts 6 months. In case of amelioration of physical, hygienic and psycho-social condition, it is possible to subsequently consider the addiction treatment.

Liver function impairment
In people administering drugs intravenously, chronic virus hepatitis often occurs. In patients with liver impairment caution is necessary when administering Methadon Molteni. Metabolism of methadone in patients with liver cirrhosis is slower and the so called first-pass effect is decreased. This often results in increased plasma level of methadone. Methadon Molteni must be administered at lower doses than normally
recommended and the patient’s reaction must be taken as a measure for further dosage.

**Kidney function impairment**
In patients with kidney impairment caution is necessary when administering Methadon Molteni. The interval between doses needs to be prolonged to 8 hours at minimum in case of glomerular filtration speed (GFS) 10-50 ml/min and to 12 hours at minimum in case of lower GFS than 10 ml/min.

**Children**
The product is not intended for use in children.

**Elderly**
Elderly or frail patient should receive the lowest possible dose. Repeated doses should only be given with extreme caution and the patient’s reaction must be taken as a measure for further dosage.

### 4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients.
- Brain trauma, increased intracranial pressure and delirium tremens.
- Heart insufficiency.
- Respiratory depression.
- Obstructive airways disease and cyanosis.
- Hypercarbia.
- Paralytic ileus.

### 4.4 Special warnings and precautions for use

**Dependence**
Methadone can cause a morphine-like drug dependence. Following repeated administrations, psychic dependence, physical dependence and tolerance can occur; therefore it must be prescribed and administered with the same caution utilized for morphine.

Extreme caution must be taken in the following cases

*Cranial lesions and high intracranial pressure.* The respiratory depressant effects of methadone and its capacity to increase the cerebrospinal fluid pressure can be considerably increased in the presence of an increase of the intracranial pressure; furthermore narcotics produce undesirable effects that can hide neurological symptoms in patients with cranial lesions.

*Asthma and other respiratory conditions.* In patients with acute asthma attacks, in those with chronic obstructive pulmonary disease or cor pulmonare and in individuals with a substantially decreased respiratory reserve in pre-existing respiratory depression, hypoxia or hypercapnia, even the usual therapeutic dosages of narcotics may reduce the respiratory drive and increase the airway resistance to the point of apnoea.

*Hepatic dysfunction or renal dysfunction.* Caution should be exercised in patients with hepatic dysfunction or renal dysfunction. As with other opioids methadone may cause troublesome constipation, which is particularly dangerous in patients with severe hepatic impairiment, and measures to avoid constipation should be initiated early.

Caution is necessary in elderly, in patients with *decreased thyroid function, myxedema, Addison’s disease, urethral stricture and prostate hypertrophy*; in these cases dosage must be decreased.

*Severe risk patients.* Suicide attempts with opiates, especially combined with tricyclic antidepressants, alcohol and other substances affecting the central nervous system, are part of the clinical features of dependency.
Children are more sensitive than adults and so intoxication may occur already with a very small dose. In patients with kidney or gall stones prophylactic administration of atropine or another spasmolytic drug is necessary.

**Hypotensive effect.** The administration of methadone can cause serious hypotension in hypovolemic subjects or with concomitant intake of medicinal products like phenothiazine or certain anaesthetics. In elderly outpatients and in patients with cardiovascular disease the risk of hypotension and syncope is increased.

**Use of narcotic antagonists.** In an individual with narcotic physical addiction, the administration of the usual dose of a narcotic antagonist can trigger an acute withdrawal syndrome. The severity of the syndrome will depend on the degree of physical dependence and on the dose of antagonist administered. The use of a narcotic antagonist in this subject should possibly be avoided. When this must be used for treatment of a severe respiratory depression in a patient physically addicted, the antagonist must be administered with extreme caution and gradually with dosages below the usual ones.

**Acute abdominal conditions.** The use of methadon or other narcotics may be confound the diagnosis or the clinical course in the patients with acute abdominal conditions.

**Cardiac arrhythmia.** As high doses of methadone are often related to torsade de pointes (QT interval prolongation) patients with risk factors for torsade de pointes must be treated with caution. Risk factors are:
- Electrolyte disturbances, especially hypokalemia, hypocalcemia and hypomagnesemia.
- Inborn or acquired QT interval prolongation.
- Cardiomyopathy, especially with heart insufficiency symptoms.
- Sinus bradycardia.
- Symptomatic alterations of heart rhythm.
- Simultaneous administration of drugs prolonging the QT interval (e.g. some antiarrhythmic drugs, neuroleptics, antibiotics, antidepressants and antihistaminic drugs).

In patients for whom the potential benefits of a methadone-based treatment outweigh the risk of tachycardia onset, an electrocardiogram must be performed before therapy begins and after two weeks of treatment, with the aim of verifying and quantifying the effect of methadone hydrochloride on the QT interval. An electrocardiogram is also recommended before increasing the dose assumed.

Methadon Molteni contains maltitol. Patients with rare hereditary problems of fructose intolerance 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 P-glycoprotein substrate; all the drugs that inhibit it (quinidine, verapamil) can increase the serum concentration of methadone. With enhanced passing through blood-brain barrier also the pharmacodynamic effect of methadone probably increases.

**CYP3A4 isoenzyme inducers:** Methadone is a substrate for cytochrome P-450 isoenzyme 3A4 (CYP3A4) (see section 5.2). With CYP3A4 induction, methadone clearance increases and methadone plasma level decreases. Inducers of this isoenzyme (barbiturates, carbamazepine, phenytoine, nevirapine, rifampicin, efavirenz, amprenavir, spiranolacton, dexamethason, hypericum perforatum (St. John’s Wort)) may stimulate liver metabolism. For instance, after three weeks of treatment with daily dose of 600 mg of efavirenz the average peak concentration of methadone and AUC in patients treated with methadone (35-100 mg daily) decreased by 48% and 57%, respectively. The effects of enzyme induction will be more significant if the inducer is added after initiation of methadone treatment. As a result of these interactions abstinence symptoms were reported, therefore, the dosage of methadone must be increased. If the treatment with CYP3A4 inducers is terminated, methadone dosage must be decreased.

**Isoenzyme CYP3A4 inhibitors:** Methadone is a substrate for cytochrome P-450 isoenzyme 3A4 (CYP3A4) (see 5.2. Pharmacokinetic properties). With CYP3A4 inhibition methadone clearance decreases. Inhibitors may cause methadone plasma level increase. CYP3A4 inhibitors are: cannabinoids, clarithromycin, delavirdine, erythromycine, fluconazole, grapefruit juice, selective serotonin reuptake inhibitors, itraconazol, ketoconazol, fluoxetine, fluvoxamine, nefazodon.
**Didanosine and stavudine:** Methadone slows down the absorption and stimulates the first-pass mechanism of stavudine and didanosine which results in decreased biological availability of stavudine and didanosine.

**Zidovudine:** Zidovudine plasma level decreases after methadone administration both in oral and intravenous administration. These effects are probably due to the inhibition of zidovudine glucuronization and, therefore, even decreased zidovudine clearance. During methadone treatment the patients must be monitored due to possible occurrence of toxic reactions to zidovudine necessitating the decrease of zidovudine dosage. Interactions of zidovudine and methadone (zidovudine is a CYP3A4 inducer) may lead to opioid abstinence symptoms in simultaneous administration of methadone and zidovudine (headache, myalgia, fatigue and irritation).

**Protease inhibitors:** In contrast to expected qualities of protease inhibitors *in vitro* (protease inhibitors actually act *in vitro* as potent CYP3A4 inhibitors), different clinical studies in patients on supplementary methadone therapy show that concomitant treatment with ritonavir in combination with other protease inhibitors, such as e.g. nelfinavir, saquinavir or lopinavir may cause a substantial decrease in methadone AUC resulting in abstinence symptoms. Mechanism of this induction effect on methadone metabolism is not known yet.

**Products influencing urine acidity:** Methadone is a weak base. Acid compounds of urine (such as ammonium chloride and ascorbic acid) may increase methadone clearance. In this case it is necessary to increase methadone dose.

**Histamine H2-antagonists:** Histamine H2-antagonists such as cimetidine, can reduce the protein binding of methadone resulting in increased opiate action.

**Abacavir:** nineteen patients entering methadone treatment were given a single dose of abacavir (600 mg), begun methadone and, after 14 days, co-administered abacavir and methadone for the following 14 days. The results showed, in the last 14 days, a statistically significant increase (23%) in the rate of clearance of methadone, but no changes in the time to peak concentration or half-life. In addition, a significant decrease (34%) in the peak concentration and increase (67%) in the time to peak concentration of abacavir were observed in the first 14 days. The introduction of abacavir and amprenavir in 5 dependent patients in methadone treatment resulted in median decrease to 35% of the original concentration of methadone, with adverse effects compatible with withdrawal reactions in two patients.

**Efavirenz:** efavirenz induces the methadone metabolism through cytochrome P4503A4. Following a three-week therapy with efavirenz, the mean peak concentrations of methadone and the AUC were reduced by 48% and 57% respectively. Efavirenz added to a patient under methadone therapy could induce a withdrawal syndrome that usually starts after two weeks of efavirenz therapy, but can go on for up to 28 days. For this reason it may be necessary to adjust the methadone dosage.

**Nevirapine:** nevirapine induces methadone metabolism through cytochrome P450 family. The co-administration of nevirapine and methadone in twenty-five human immunodeficiency virus-infected subjects significantly decreased the mean dose-adjusted AUC of methadone by 41%. Methadone dose adjustments are justified when methadone is coadministered with nevirapine.

**Pharmacodynamic interaction**

**Opioid agonists/antagonists:** Opioid antagonists (naloxone and naltrexone) antagonize the methadone action and provoke a withdrawal syndrome. Partial agonists/antagonists (as nalbufine and pentazocine) may intensify neurologic respiratory suppressive and hypotensive effects of methadone. When these substances are used in combination with methadone, they may cause and aggravate neurological, respiratory and hypotensive effects. Agonist or antagonist effects depend on methadone dose and are more frequent in case of low or medium methadone doses. These substances may cause abstinence syndrome in case of long-term administration.

**MAOIs:** The concurrent use Monoamine oxidase inhibitors (MAOIs) may prolong and enhance the respiratory depressant effects of methadone.

**Substances suppressing CNS activity:** Substances with suppressive effect on the CNS may increase respiration depression; it is therefore necessary to decrease the dose of one or both substances.

**Antidiarrhoeals:** Concomitant administration of methadone and antidiarrhoeals (diphenoxylate and loperamide) may cause severe constipation and increase CNS depression. Opioid analgesics in combination with antimuscarinic substances may lead to severe constipation or paralytic ileus, especially in case of long-term administration.

**Alcohol:** may cause severe respiration depression and hypotension.
**Octreotide**: can reduce the analgesic effect of methadone and morphine, therefore if a reduction or loss of pain control occurs octreotide suspension has to be taken into consideration.

### 4.6 Fertility, pregnancy and lactation

Limited information on methadone use in pregnancy does not indicate increased risk of inborn abnormalities. In infants whose mothers were undergoing long-term methadone treatment abstinence symptoms/respiration depression may occur. Data from animal studies show reproduction toxicity (see section 5.3). It is generally recommended not to perform patient detoxification especially after 20th week of pregnancy; however, supportive methadone treatment is recommended. Use of methadone oral solution shortly before or during parturition is not recommended due to the risk of neonatal respiration depression. Methadone is excreted into breast milk and may cause respiratory depression in the newborn. Breast feeding is usually not recommended. A careful risk benefit assessment case by case is suggested.

### 4.7 Effects on ability to drive and use machines

Methadone negatively influences the ability to drive motor vehicles and operate machinery. Patients using methadone must not participate in traffic operations.

### 4.8 Undesirable effects

The following table summarises adverse drug reactions of methadone divided into groups according to MedDRA terminology together with their frequency: 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):

<table>
<thead>
<tr>
<th>MedDRA system organ class</th>
<th>Frequency</th>
<th>Undesirable effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Investigations</td>
<td>Uncommon to rare</td>
<td>Blood prolactin increased (on long-term administration)</td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td>Very common to common</td>
<td>Bradycardia, palpitations</td>
</tr>
<tr>
<td></td>
<td>Uncommon to rare</td>
<td>Shock, cardiac arrest, torsade de pointes (in high doses), extrasystole, prolonged QT interval</td>
</tr>
<tr>
<td>Blood and lymphatic system disorders</td>
<td>Uncommon to rare</td>
<td>Haemorrhagia</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Very common to common</td>
<td>Euphoria, dysphoria, headache, dizziness, sedation, insomnia, agitation, disorientation, feeling of empty head, rushing</td>
</tr>
<tr>
<td>Eye disorders</td>
<td>Very common to common</td>
<td>Visual disturbances, miosis</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>Very common to common</td>
<td>Respiratory depression, respiratory acidosis</td>
</tr>
<tr>
<td></td>
<td>Uncommon to rare</td>
<td>Respiratory arrest</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Very common to common</td>
<td>Nausea, vomiting, constipation, dry mouth</td>
</tr>
<tr>
<td>Renal and urinary disorders</td>
<td>Very common to common</td>
<td>Urinary retention and difficulty to urinate, antidiuretic effect</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Very common to common</td>
<td>Excessive sweating, itchiness, nettle rash, other skin reactions, oedema</td>
</tr>
<tr>
<td></td>
<td>Uncommon to rare</td>
<td>Hemorrhagic nettle rash</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td>Very common to common</td>
<td>Anorexia</td>
</tr>
</tbody>
</table>
Vascular disorders | Very common to common | Orthostatic hypotension (in higher doses) and syncope, fainting |
---|---|---|
General disorders and administration site conditions | Very common to common | Oedema |
Reproductive system and breast disorders | Very common to common | Libido reduction and/or sexual impotence |
Hepatobiliary disorders | Very common to common | Spasms of the biliary tract |

Long-term administration leads to dependency to the same extent as in other opioid agonists. Symptom intensity is, however, weaker than the intensity caused by heroine or morphine. The time necessary for dependency disappearance is longer than in heroine due to longer half-life.

4.9 Overdose

Intoxication symptoms
Respiration depression, central nervous system depression (from stupor to coma), hypothermia, bradycardia, hypotension and shock.

Intoxication treatment
During methadone administration the patient must be, if necessary, provided artificial breathing and naloxone is used as an antidote. Naloxone dosage is 5-10 µg/kg intravenously, it may be repeated every 10-20 minutes if necessary. With regard to long methadone half-life and short naloxone half-life more frequent antidote administration is necessary.

5. PHARMACOLOGICAL PROPERTIES

Pharmacoterapeutic group: Drug used in opioid dependence.
ATC code: N07BC02.

5.1 Pharmacodynamic properties

Methadone is an opioid agonist affecting predominantly µ-receptor. The analgesic effect of the racemate is almost entirely due to its l-isomer, which is at least 10× more potent as an analgesic than the d-isomer. The d-isomer lacks significant respiratory depressant activity, but does have anti-tussive effects. Methadone also acts as an κ and σ opioid receptor agonist. This action causes analgesia, respiration depression, cough suppression, nausea and vomiting (via an effect on chemoreceptor trigger zone) and constipation. En effect on the oculomotor nerve nucleus and probably also on opioid receptors in the pupillary muscles causes pupillary constriction. All these effects are reversible by naloxone with pA2 value similar to its morphine antagonism. It leads to „the morphine type“ dependency.

5.2 Pharmacokinetic properties

Absorption
Methadone is a basic lipophilic substance which is almost completely absorbed in gastrointestinal tract. Tmax varies between 1.5-3 hours. Biological availability amounts to more than 80%. Steady state is achieved in 5-7 days. Distribution volume of methadone is about 5 l/kg.

Distribution
Pharmacokinetic profile of methadone shows a wide distribution. Approximately 89% of methadone inside the organism is bound to proteins. In the plasma methadone binds predominantly to alpha-1-glycoprotein. Methadone binding to extravascular proteins in tissues is strong and methadone accumulates in the liver, kidney and other organs. As methadone transfer from peripheral tissues to central circulation is slow,
methadone clearance is prolonged. Methadone passes through the placenta and into breast milk.

Metabolism
Methadone is mainly metabolized by N-demethylation (oxidation) enzymes in liver. Two eminent metabolites, 2-ethyliden-1,5-dimethyl-3,3-diphenylpyrroldine (EDDP) and 2-ethyl-5-methyl-3,3-difenylpyraline (EMDP), are biologically inactive. Methadone is predominantly a substrate for cytochrome P450 isoenzyme (CYP) 3A4 and, to a lesser extent, for CYP 2D6 and CYP 2B6. Many interactions are due to CYP enzyme induction or inhibition (see section 4.5).

Elimination
Methadone elimination shows great interindividual variability. Methadone elimination half-life estimates range in different studies from 19 to 55 hours. In studies with long-term methadone administration a relatively short half-life is observed due to autoinduction of elimination. Methadone clearance is not dose related. During 96 hours, 15-60% of methadone total dose is excreted to urine. The other fractions are excreted mainly to gall. The ratio of renal clearance corresponds predominantly to urine acidity. In case of lower urine pH more methadone is excreted.

Special groups of patients
As far as kinetic parameters of methadone are concerned, no differences between male and female patients were found. In elderly patients (> 65 years) methadone clearance decreased only to a small extent.

5.3 Preclinical safety data
In high doses methadone caused inborn abnormalities in guinea pigs, hamsters and mice, exencephaly and central nervous system defects were most frequently reported. Accidentally, rachischisis in cervical region was reported. In chicken embryos lack of neural tube closing was reported. In rats and rabbits methadone did not show teratogenic effects. Besides that, a lower number of cubs was reported in rats, and higher mortality of cubs, growth retardation, neurological alterations of behaviour and lower brain weight were found. In mice, decreased ossification of fingers, sternum, and skull, as well as a lower number of embryos per litter was reported. Carcinogenicity has not been studied.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Liquid maltitol
Sodium benzoate Sodium citrate dihydrate
Sodium saccharin
Citric acid anhydride
Water, purified.

6.2 Incompatibilities
Methadone hydrochloride is not compatible with hydroxybenzoate conservation preparations. Simultaneous use of Methadon Molteni oral solution and syrups conserved with hydroxybenzoate is not recommended.

6.3 Shelf life
3 years

6.4 Special precautions for storage
This medicinal product does not require any special storage conditions.
Shelf life after opening:
50 ml bottle - 7 days.
1000 ml bottle - 28 days.

6.5 Nature and contents of container

Bottle 10 ml
Brown glass bottle (hydrolytic class III), childproof screw cap consists of outer cap (material PP white) and inner screw part for cap (material PP transparent), paper folding box, label, measuring device — all components which are in contact with solution are made of PE, package information leaflet.

Bottle 50 ml
Brown glass bottle (hydrolytic class III), childproof screw cap consists of outer cap (material PP white) and inner screw part for cap (material HDPE transparent), paper folding box, label, measuring device — all components which are in contact with solution are made of PE, package information leaflet.

Bottle 1000 ml
Brown glass bottle (hydrolytic class III), childproof screw cap consists of outer cap (material PP white) and inner screw part for cap (material HDPE transparent) and liner (material PE white, label, package information leaflet).

6.6 Special precautions for disposal and other handling

Methadone hydrochloride falls under Opium Law.

7. MARKETING AUTHORIZATION HOLDER

[To be completed nationally]

8. MARKETING AUTHORIZATION NUMBER(S)

[To be completed nationally]

9. DATE OF FIRST AUTHORIZATION/ RENEWAL OF THE AUTHORIZATION

[To be completed nationally]

10. DATE OF REVISION OF THE TEXT

DD/MM/YYYY
LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING (10 ML)

1. NAME OF THE MEDICINAL PRODUCT

Methadon Molteni 5 mg/ml oral solution
Methadone hydrochloride

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Methadone hydrochloride 5 mg in 1 ml.

3. LIST OF EXCIPIENTS

Maltitol liquid

4. PHARMACEUTICAL FORM AND CONTENTS

10 ml oral solution

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP:

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Return the unused drug into the pharmacy.
11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

[To be completed nationally]

12. MARKETING AUTHORISATION NUMBER(S)

Reg. No.:

13. BATCH NUMBER

Batch:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to special medical prescription.

15. INSTRUCTION ON USE

16. INFORMATION IN BRAILLE

Methadon Molteni
**MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNIT (10 ML)**

**ETIQUETTE**

<table>
<thead>
<tr>
<th>1. NAME OF THE MEDICINAL PRODUCT AND ROUTE OF ADMINISTRATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methadon Molteni 5 mg/ml oral solution</td>
</tr>
<tr>
<td>Methadone hydrochloride</td>
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<table>
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<tr>
<th>2. METHOD OF ADMINISTRATION</th>
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<td>Oral use.</td>
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<th>3. EXPIRY DATE</th>
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<th>4. BATCH NUMBER</th>
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<td>Batch:</td>
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<table>
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<tr>
<th>5. CONTENT BY VOLUME</th>
</tr>
</thead>
<tbody>
<tr>
<td>10 ml</td>
</tr>
</tbody>
</table>
PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKING (50 ML)

(ETIQUETTE)

1. NAME OF THE MEDICINAL PRODUCT

Methadon Molteni 5 mg/ml oral solution
Methadone hydrochloride

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Methadone hydrochloride 5 mg in 1 ml.

3. LIST OF EXCIPIENTS

Maltitol liquid

4. PHARMACEUTICAL FORM AND CONTENTS

50 ml oral solution

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY
8. EXPIRY DATE

EXP:

9. SPECIAL STORAGE CONDITIONS

Shelf life after first opening: 7 days.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Return the unused drug into the pharmacy.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

[To be completed nationally]

12. MARKETING AUTHORISATION NUMBER(S)

Reg. No.:

13. BATCH NUMBER

Batch:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to special medical prescription.

15. INSTRUCTION ON USE

16. INFORMATION IN BRAILLE

Methadon Molteni
PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING (1000 ML)

ETIQUETTE

1. NAME OF THE MEDICINAL PRODUCT

Methadon Molteni 5 mg/ml oral solution
Methadone hydrochloride

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Methadone hydrochloride 5 mg in 1 ml.

3. LIST OF EXCIPIENTS

Maltitol liquid

4. PHARMACEUTICAL FORM AND CONTENTS

1000 ml oral solution

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP:

9. SPECIAL STORAGE CONDITIONS

Shelf life after first opening: 28 days.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE
Return the unused drug into the pharmacy.

<table>
<thead>
<tr>
<th>11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER</th>
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<tbody>
<tr>
<td>[To be completed nationally]</td>
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<table>
<thead>
<tr>
<th>12. MARKETING AUTHORISATION NUMBER(S)</th>
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<tr>
<td>Reg. No.:</td>
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<table>
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<th>13. BATCH NUMBER</th>
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<td>Batch:</td>
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<table>
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<tr>
<th>14. GENERAL CLASSIFICATION FOR SUPPLY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medicinal product subject to special medical prescription.</td>
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</tbody>
</table>
Read all of this leaflet carefully before you start taking using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible effects not listed in this leaflet.

What is this leaflet:
1. What Methadon Molteni is and what it is used for
2. What you need to know before you take Methadon Molteni
3. How to take Methadon Molteni
4. Possible side effects
5. How to store Methadon Molteni
6. Contents of the pack and other information

1. What Methadon Molteni is and what it is used for

Methadon Molteni is used for:
- treatment of abstinence symptoms of heroin /opiates aimed at detoxification.
- supplementary treatment of people dependent on opiates who are unable to stop using opiates.

2. What you need to know before you take Methadon Molteni

Do not take Methadon Molteni
- if you are allergic to methadone (active substance) or any of the other ingredients of Methadon Molteni,
- if you have a respiratory ailment,
- if you have had or are having difficulty in breathing,
- if you are suffering from heart insufficiency,
- if you have recently suffered a head injury,
- if you have raised pressure within your skull,
- if you suffer from delirium tremens (withdrawal syndrome in chronic alcohol abusers characterized with hallucinations, shakes, seizures).
- if you suffer from blockage of the intestine causing colic, vomiting, and constipation (paralytic ileus)

Warnings and precautions
Talk to your doctor or pharmacist before you start to take Methadon Molteni
- if you have kidney or gall stones,
- if you are elderly or suffer from heart and blood vessels disease (e.g. atherosclerosis); in this case you have an increased risk of low blood pressure and sudden loss of consciousness,
- if you have kidney or liver disease,
- if you are suffering from underactive thyroid gland or hyperactive adrenal gland,
- if you are a man who suffers from prostate problems,
- if you are elderly,
- if you are suffering from heart beating alterations, heart muscle disease, you have low blood level of
potassium, calcium or magnesium.

Methadon or other narcotics may mask acute abdominal conditions. If you suffer from symptoms of acute abdominal conditions such as a sudden, severe pain in the abdomen with tenderness, and muscular rigidity consult the next administration of methadon with your doctor.

**Other medicines and Methadon Molteni**

Please inform your doctor or pharmacist if you are taking/using other medicines, have recently taken or might take other medicines.

If you are taking any of the following medicines, you must talk to your doctor before taking this medicine:
- Antibacterials (rifampicin, clarithromycin, erythromycin),
- Antifungals (fluconazole, itraconazole, ketoconazole),
- Antivirals (nevirapine, delavirdine, didanosine, stavudine, zidovudine, ritonavir, abacavir, efavirenz),
- Antidiarrhoeals (diphenoxylate, loperamide),
- Anticonvulsant (barbiturates, phenytoin, carbamazepine),
- Antipsychotic, antianxiety and antidepressants, monoamine oxidase inhibitors (MAOIs, used for the treatment of depression or Parkinson’s disease) (fluoxetine, paroxetine, sertraline, nefazodone, fluvoxamine),
- Strong painkiller e.g. morphine,
- Naloxone, naltrexone, buprenorfine, butorphanol, nalbuphine, pentazocine, octreotide,
- Cannabinoids,
- Antiarrhythmic drugs (used to treat heart rhythm problems quinidine, verapamil),
- Antiallergic drugs,
- Spironolacton, dexamethason,
- Hypericum perforatum (St. John’s Wort)
- Histamine H2-receptor antagonists used such as cimetidine (for the treatment of peptic ulcers).

**Taking Methadon Molteni with food, drink and drink alcohol**

You must not take alcohol or drink grapefruit juice whilst taking this medicine.

**Pregnancy and breast-feeding and fertility**

If you are pregnant or breast-feeding think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

You should not take Methadon Molteni if you are going into labour or are in labour. Always consult your pregnancy with your doctor.

During breast feeding methadone will pass on to the baby via the milk. This may be permissible if your doctor consider it safe in your particular circumstance.

**Driving and using machines**

Methadone negatively influences the ability to drive motor vehicles and operate machinery. Patients using methadone must not participate in traffic operations.

Methadon Molteni contains maltitol

If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product.

3. How to take Methadon Molteni

Always take this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

Do not take more or less than the stated dose. Do not take it more or less often than prescribed. Do not take it for a longer time than your doctor prescribed.

Methadon Molteni is to be taken by mouth.
1 ml of Methadon Molteni solution contains 5 mg of methadon. Methadon Molteni (10 and 50 ml package) is provided with dosing pipette calibrated from 0.5 ml (2.5 mg of methadon) to 3 ml (15 mg of methadon). Higher doses should be measured by multiple use of dosing pipette. 1000 ml package is intended only for specialized treatment centers and therefore is without dosing pipette.

**Treatment of abstinence symptoms**
The usual initial daily dose is 20 mg (corresponding to 4 ml of oral solution) usually slowly increasing to 30-50 mg per day (corresponding to 6 ml – 10 ml of oral solution). The dose may be in the course of few weeks gradually decreased.
Your doctor will determine the dose according to the seriousness of abstinence symptoms and your reaction on the treatment.

**Supplementary treatment**
Initial dose may be determined as in case of addiction treatment. Usual daily dose is then 50 - 100 mg (corresponding to 10 ml - 20 ml of oral solution), mostly about 60 mg (corresponding to 12 ml of oral solution). Treatment usually lasts 6 months. In case of amelioration of problems, it is possible to subsequently consider the addiction treatment.

**Liver function impairment**
In patients with liver impairment caution is necessary when administering Methadon Molteni. Methadon Molteni must be administered at lower doses than normally recommended and the patient’s reaction must be taken as a measure for further dosage.

**Kidney function impairment**
In patients with kidney impairment caution is necessary when administering Methadon Molteni. The interval between doses needs to be prolonged according to the patient’s health state.

**Children**
The product is not intended for use in children.

**Elderly**
Elderly or frail patient should receive the lowest possible dose. Repeated doses should only be given with extreme caution and the patient’s reaction must be taken as a measure for further dosage.

**If you take more Methadon Molteni than you should**
Immediately call for the doctor in case of overdosing or at any occasional intake by a child. As children are more sensitive than adults and so intoxication may occur already with a very small dose.
Intoxication symptoms include:
Breathing difficulties, stupor, profound state of unconsciousness (coma), low body temperature, decreased heart rate, low blood pressure and shock.

**If you forget to take Methadon Molteni**
If you miss a dose, do not take this medicine when you remember. Wait until the next dose is due then take only one dose. Do not take a double dose to make up for a forgotten dose.

**If you stop taking Methadon Molteni**
Do not stop taking Methadon Molteni unless your doctor tells you to due to the risk of withdrawal symptoms. It should not be stopped abruptly and your doctor will reduce your dose gradually.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

### 4. Possible side effects
Like all medicines, this medicine can cause side effects, although not everybody gets them.
During the administration of methadone following side effects may occur (ranged according to their occurrence):

**Very common to common (possible occurrence in more than 1 patient out of 100):** mood changes, headache, dizziness, sedation, visual disturbances, constriction of the pupil (miosis), breathing difficulties, nausea, vomiting, constipation, dry mouth, swelling, sudden fall in blood pressure that occurs when a person assumes a standing position, usually after a prolonged period of rest and when using higher doses, fainting, slow heartbeat, awareness of heart beating, sleeplessness, restlessness, desorientation, feeling of empty head, sudden burst of emotion, difficulties to urinate, loss of appetite for food, edemas, libido reduction or inability to achieve or maintain an erection, spasm of bile duct.

**Uncommon to rare (possible occurrence in more than 1 patient out of 10 000, but less than 1 patient out of 100):** irregular heart beat (when using high doses of the product) extrasystole (form of irregular heartbeat), prolonged QT interval (heart condition which can be associated with fainting and irregular heart beat), sudden complete cessation of respiratory movement, sudden cessation of cardiac function resulting in loss of effective circulation, increased level of hormon prolactin in blood, bleeding, nettle rash.

Long-term administration leads to dependency (its intensity is, however, weaker than the intensity caused by heroine or morphine).

If you get any side effects, talk to your doctor or pharmacist. This includes any possible effects not listed in this leaflet.

### 5. How to store Methadon Molteni

Keep this medicine out of the sight and reach of children.  
This medicinal product does not require any special storage conditions.  
Expiration time after first opening is 7 days for 50 ml bottle, and 28 days for 1000 ml bottle.  
Do not use Methadon Molteni after the expiry date which is stated on the label after EXP. The expiry date refers to the last day of that month.

### 6. Content of the pack and other information

**What Methadon Molteni contains**  
The active substance is methadone hydrochloride 5 mg in 1 ml.  
The other ingredients are:  
Liquid maltitol, Sodium benzoate, Sodium citrate dihydrate, Sodium saccharin, Citric acid anhydrate, Purified water.

**What Methadon Molteni looks like and contents of the pack**  
Colourless to slightly yellow solution.  
Bottle size: 10 ml, 50 ml and 1000 ml.  
Not all bottle sizes may be marketed.

**Marketing Authorisation Holder**  
[To be completed nationally]

**Manufacturer**  
Zentiva ka.s., Hlohovec, Slovak Republic.

This leaflet was last revised in MM/YYYY