METADONE CLORIDRATO MOLTENI

Methadone hydrochloride 5 mg/ml oral solution

COMPOSITION

1 ml of oral solution contains 5 mg methadone hydrochloride.
Excipients: sucrose, glycerol, sodium benzoate, lemon flavour, citric acid, purified water.

PHARMACEUTICAL FORM AND CONTENTS

Oral solution.
Multidose bottle of 1000 ml oral solution, supplied with a measuring cup graded 1-2-3-4-5-6 ml corresponding to 5-10-15-20-25-30 mg of methadone hydrochloride.

PHARMACOTHERAPEUTIC GROUP

Drugs used in opioids dependence, ATC code N07BC02.

MARKETING AUTHORIZATION HOLDER AND MANUFACTURER

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THERAPEUTIC INDICATIONS

- Severe pain in patients who no longer respond to sequential treatment with other analgesics, non-steroidal-anti-inflammatory-drugs or weaker opioids.
- Treatment of opioid drug addiction. Detoxification and maintenance treatments must be carried out under medical control. If methadone is administered for treatment of opioid drug addiction for more than three weeks, the procedure passes on from the treatment of acute abstinence syndrome to maintenance therapy.

CONTRAINDICATIONS

Hypersensitivity to the active substance or to any of the excipients. Serious constipation. Organic heart diseases. Severe hepatic and kidney failure. Non-compensated diabetes. Porphyria. Hypotension. Intracranial hypertension. Craneoencephalic trauma. Acute asthma attack. Chronic obstructive airways disease. Respiratory failure. Cor pulmonale. Hypovolemia. Methadone is generally contraindicated during pregnancy and lactation, except in the cases indicated in the Section "Pregnancy and Lactation". Methadone is not indicated for obstetric analgesia since its prolonged duration of action increases the risk of neonatal depression. Methadone is contraindicated in children.

SPECIAL WARNING AND PRECAUTION FOR USE

Special risk patients. Methadone must be administered with caution and the initial dose must be reduced in elderly and debilitated patients and patients with hypothyroidism, Addison's disease, prostatic hypertrophy, urethral stricture.
During treatment with methadone, prolongation of the QT-interval and torsade de pointes have been reported, particularly at high doses (> 100 mg/day). Methadone should be administered with caution in patients at risk for onset of prolongation of the QT-interval, for example positive anamnesis to QT-prolongation, cardiac disorders at an advanced stage, concurrent treatment with medications that may prolong the QT-interval.

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

Interaction with other central nervous system depressors. Methadone must be utilized with caution and at reduced dosages in patients who receive at the same time other narcotic analgesics, general anaesthetics, phenothiazine, other hypnotic sedative tranquillisers, tricyclic antidepressants and other suppressors of the central nervous system, including alcohol. Depression and deep sedation or coma can occur.

Anxiety. Methadone does not have any anti-anxiety activity; therefore symptoms of anxiety which appear during the treatment must not be treated by increasing the dose of methadone.

Cranial lesions and elevated 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 (see section: Contraindications).

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 (see section: Contraindications).

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

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.

Outpatient use. In outpatients methadone may cause orthostatic hypotension.

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.

For who does sports. Use of this medicine without therapeutic needs constitutes doping. It can give a positive result in the dope tests also at therapeutic doses.

Information about some of the ingredients. Metadone Cloridrato Molteni contains sucrose: 1 ml of oral solution contains 0.4 g of sugar. The maximum daily dosage (24 ml, corresponding to 120 mg of methadone hydrochloride) implies the intake of 9.6 g of sugar; therefore, it is not indicated for patients suffering from hereditary fructose intolerance, from disturbances in sugars absorption (glucose/galactose) of from insufficiency in enzymes needed for digestion of sugars (sucrase/isomaltase). This should be also taken into account in patients suffering from diabetes.

INTERACTIONS

Pharmacokinetic interactions

Methadone is a P-glycoprotein substrate, therefore all the drugs that inhibit it (quinidine, verapamil) can increase serum concentration of methadone.

Methadone is metabolised by the CYP3A4 isoenzyme. The inducers of this isoenzyme (barbiturics, carbamazepine, phenytoin, nevirapine, rifampicin) can induce the methadone hepatic metabolism, which could be more significant if the inducer is added after the methadone therapy has started. Following such interactions withdrawal symptom cases have been reported, therefore it was necessary to increase the dosage of methadone.

When the CYP3A4 inducing drugs therapy is suspended, the dosage of methadone must be reduced. The CYP3A4 inhibitors (cannabinoid, clarithromycin, delavirdine, erythromycin, fluconazole, grapefruit juice, serotonin recapture selective inhibitors, itraconazole, ketoconazole, nefazodone) can provoke an increase in methadone concentration.

Methadone excretion is reduced in case of co-administration of drugs inhibiting CYP3A4, such as some anti-HIV agents, macrolides, cimetidine, azole antifungal agents (since methadone is metabolised by the CYP3A4 isoenzyme).

Methadone reduces the AUC and Cmax of the didanosine and of the stavudine, reducing the bioavailability of these drugs. Besides, methadone can slow down the absorption and increase the first passage metabolism of the afore mentioned drugs.

Methadone increases the plasmatic concentration of zidovudine for both oral and intravenous administration, and also provokes an increase in the AUC of zidovudine for oral administration, more than for intravenous administration. Such effects are due to the inhibition of the glucoronidation of zidovudine and it's reduced kidney clearance. During treatment with methadone, the patients have to be monitored for a possible zidovudine toxicity, whereby it could be necessary to reduce the zidovudine dosage. The patients that take both drugs can develop typical symptoms of opioid withdrawal syndrome (cephalea, myalgia, fatigue and irritability). The antiretroviral protease inhibitor can inhibit the metabolism of methadone at several degrees, but the more significant reactions are obtained with ritonavir, while a possible interaction with abacavir, in general, does not require dosage adjustments. 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. There are indications that suggest that if efavirenz is added to a patient in therapy with methadone, a withdrawal syndrome could develope 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 dosage.

Methadone is a weak base. Urine acidifiers (ammonium chloride) can increase methadone kidney clearance. In this situation the methadone dosage should be increased.

Pharmacodinamics interactions

The opioid antagonists (naloxone and naltrexone) carry out a pharmacological action contrary to the methadone one. These drugs can block the methadone action and provoke a withdrawal syndrome.

The agonists/antagonists (butorphanol, nalbuphine, pentazocine) can partially block the analgesia, respiratory depression and central nervous system (CNS) depression due to methadone. Used at the same time it can provoke and increase neurological, respiratory and hypotensive effects. The additive or antagonist effects depend on the methadone dosage and are more frequent when the methadone dosage is low or moderate. These drugs can cause withdrawal syndrome in patients in chronic therapy.

Using at the same time methadone with drugs with a depressive action on the CNS can provoke an increase of respiratory depression, therefore it may be necessary to decrease the dosage of one or both drugs.

Cardiac disturbances may occur in patients concomitantly treated with methadone and medicines affecting cardiac transmission or electrolytic balance. In such circumstances, it may be useful to perform an electrocardiogram.

The concomitant use of methadone and antidiarrheals (diphenoxylate and loperamide) can cause severe constipation and an increase depression of the CNS. Opioid analgesics, combined with antimuscarinic drugs can cause severe constipation or paralytic ileum, especially with chronic use. Octreotide can reduce the analgesic effect of methadone and morphine, therefore if a reduction or loss of the pain control occurs octreotide suspension has to be taken into consideration.

PREGNANCY AND LACTATION

Pregnancy

A careful risk benefit assessment should be made before administration to pregnant women. If there is an evident inability of the pregnant woman to withdraw from opioids, the doctor can decide to start a methadone maintenance treatment that should to be prolonged until the end of pregnancy with a stable dosage in order to avoid possible withdrawal symptoms in the mother and foetus. Methadone dosage may be increased during the last phases of pregnancy to keep the drug level adequate and therefore avoid possible therapy abandonment. If necessary, dosage reduction should occur very slowly to avoid withdrawal symptoms. Suspension of the treatment will require specialised care from obstetric staff and must not be carried out before the 14th week and not after the 32nd to avoid risk of abortion and premature delivery, respectively.

Lactation

Methadone is excreted in breast milk and may cause respiratory depression in the newborn. Breast feeding is usually not recommended. However, a careful risk benefit assessment case by case is suggested, taking into account that methadone could prevent the possibility of an overdose syndrome in the newborn.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Methadone can alter the mental and/or physical capacities necessary for potentially dangerous activities such as driving or using machines. The patient therefore must be informed. The time after which such activities may be safely resumed is extremely patient-dependent and must be decided by the physician.

POSOLOGY AND METHOD OF ADMINISTRATION

Metadone Cloridrato Molteni is a solution of methadone hydrochloride for oral use only. It must not be used for injections.

Severe pain

In order to relieve pain, the dosage must be regulated according to the severity of pain and the patient response. Occasionally, in cases of exceptionally intense pain or in patients who have become tolerant to the analgesic effect of narcotics, it can be necessary to exceed the usual recommended dosage. The average dosage for adults varies from 5 to 20 mg (1 to 4 ml) one or more times a day, according to the medical indications.

Treatment of opioid drug addiction

Metadone Cloridrato Molteni will be administered on a daily basis in accordance with medical evaluation and the treatment protocol. One treatment cycle of detoxification is not more than 21 days long and will not be repeated before 4 weeks after the conclusion of the previous cycle. The dosage schemes reported further on are recommended but can be changed in accordance with clinical assessment. Initially, one single dosage of 15 to 20 mg (3 to 4 ml) will be frequently sufficient to suppress the withdrawal symptoms. More methadone can be administered if the withdrawal symptoms are not eliminated or reoccur. When the patients are physically dependent on high dosages, it may be necessary to exceed these levels. Usually 40 mg (8 ml) a day in single or divided dosages are an adequate dosage level. The stabilization may continue for 2 – 3 days then the amount of methadone is gradually reduced. The frequency at which the methadone is reduced is determined individually for each patient. In hospitalised patients, a daily reduction of 20% of the total dosage pro die is usually well tolerated. In outpatients, a slower reduction protocol can be necessary.

If methadone is administered for more than three weeks, the procedure is no longer considered detoxification or treatment of the acute syndrome of withdrawal, but a maintenance treatment, even if the goal and intent is the eventual complete withdrawal. In the case of opioids users with ascertained stabilized addiction, maintenance treatment can be carried out when previous multidisciplinary interventions have not given positive results. This treatment is also suitable for patients with ascertained opioids addiction and HIV infection, in compromised immune syndroms or clear AIDS if the doctor believes that another kind of treatment has less chances of abstention from the use of opioids.

The replacement therapy, if well carried out, is able to eliminate "craving", that is the compulsive search for heroin, and dominate the anxiety of the drug addict. It is not necessary to carry out checks using the naloxone systemic test, for use on people with a strong addiction to heroin known to the sanitary centre, but it is certainly essential to look for morphinic related compounds in the body fluids. It should be underlined that the urine analysis to check for presence of narcotic drugs and psychotropic substances is an integral part of the treatment with methadone. Excessive use of alcohol must also be checked. If the urine test is positive to opioids, it is essential to re-evaluate the case. The dosage has to be defined by the doctor case by case, so the need for heroin is prevented, keeping into account the psychophysical condition and related pathologies of the patient. During the phase of maintenance some patients get the same dose of methadone; for others instead the dose has to be periodically modified to more or less. In any case the dose must be set so that the therapeutic effect will last over a period of at least 24 hours. By way of example, please consider that most patients take daily doses between 50 and 120 mg (10 - 24 ml), depending on their tolerance level and the ability to metabolise the medicine.

Warning: discontinuation of therapy not planned nor controlled by the physician may precipitate an acute withdrawal syndrome.

OVERDOSE

Symptoms

Following relevant overdose of methadone, respiratory depression (diminished respiratory frequency and/or of the vital capacity, Cheyne-Stokes respiration, cyanosis) occurs, extreme somnolence progressing to stupor or coma, noticeable miosis, skeletal muscle flaccidity, cold and clammy skin and sometimes bradycardia and hypotension.

In severe overdose, especially intravenously, apnoea, circulatory collapse, cardiac arrest and death can occur.

Treatment

Adequate respiratory exchange, freeing the airway and the establishing of an adequate support ventilation must be assured. If a non-tolerant person, especially a child, mistakenly takes or ingests a large dosage of methadone, effective narcotic antagonists which counteract the respiratory depression that is potentially lethal are available. The physician must therefore keep in mind that methadone is a long acting depressant (36 to 48 hours), while the antagonists used for overdose treatment are effective for briefer periods (1 to 3 hours). Therefore the patient must be kept under continuous observation in to ascertain a reoccurrence of respiratory depression and must be repeatedly treated with the antagonist of the narcotics as needed. The use of other respiratory stimulants is not indicated if the diagnosis is exact and the respiratory depression is caused exclusively by the overdose of methadone. An antagonist should not be administered in the absence of clinically significant respiratory or cardiovascular depression. The narcotics antagonist administered intravenously (naloxone, nalorphine and levallorphan) are the primary medicinal products for elimination of the intoxication symptoms. These medicinal products must be repeatedly administered up until the conditions of the patient remain satisfactory. When using naloxone, the risk that the narcotics antagonist further depresses the respiration is less probable. Oxygen, intravenous fluids, vasopressors and other supportive measures should be used when indicated.

UNDESIRABLE EFFECTS

The most frequently reported side effects are feeling empty-headed, dizziness, sedation, nausea, vomiting, perspiration and orthostatic hypotension.

Other undesirable effects are:

- Respiratory system: respiratory depression. Rarely, respiratory arrest.

- Central nervous system: euphoria, dysphoria, weakness, headache, insomnia, agitation, disorientation, visual disturbances, miosis.
- Gastrointestinal tract and liver: xerostomia, anorexia, constipation and spasms of the biliary tract.
- Cardiovascular apparatus: rushing, bradycardia, palpitations, fainting and syncope. Rarely, shock and cardiac arrest. Prolongation of the QT-interval and torsade de pointes can also occur with high doses.
- Urinary-genital apparatus: urinary retention and difficulty to urinate, anti-diuretic effect, libido reduction and/or sexual impotence.
- Skin and annexes: itchiness, nettlerash, other skin reactions, oedema and rarely hemorrhagic nettlerash.
- Possible undesirable effects due to excipients: Metadone Cloridrato Molteni contains the following excipient that may cause undesirable effects: glycerol. At the highest dosages, it may cause headache, stomach upset and diarrohea.

The patient should inform the doctor or the pharmacist of any side effects not listed in this leaflet.

EXPIRY DATE AND STORAGE

Do not use the medicine after the expiry date which is stated on the label.

Store in the original package in order to protect from light.

Keep out of the reach and sight of children.

Once the bottle is opened, the product should be used within 12 months.

This leaflet was last revised in April 2011.

METADONE CLORIDRATO MOLTENI

Methadone hydrochloride

5 mg/ml oral solution

1000 ml bottle

Composition: 1 ml of oral solution contains 5 mg methadone hydrochloride.
Excipients: sucrose, glycerol, sodium benzoate, lemon flavour, citric acid, purified water.
See leaflet for further information.
Method of administration: read the package leaflet before use.
KEEP OUT OF THE REACH AND SIGHT OF CHILDREN
Store in the original package to protect from light.
Once opened, use within 12 months.
Any unused product or waste material should be disposed of in accordance with relevant regulations.
Marketing Authorisation Holder:
L. Molteni & C. dei F.lli Alitti Società di Esercizio S.p.A.
Strada statale 67, Fraz. Granatieri, Scandicci (Firenze), Italy.

Medicinal product subject to medical prescription.

MOLTENI
FARMACEUTICI

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