SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF MEDICINAL PRODUCT

Metadon Alkaloid 10 mg/ml oral solution

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml oral solution contains 10 mg of methadone hydrochloride.

Excipient(s) with known effect: sorbitol 300 mg/ml.
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

* Oral solution

Clear, colourless solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

For use in the treatment of opioid drug addiction (as a narcotic abstinence syndrome suppressant).

4.2 Posology and method of administration

For oral administration.

Adults

Dosage must be individualized according to the individual patient's response, because of the specific methadone pharmacokinetic profile.
When methadone is used to initiate maintenance treatment, a heavy user of opiate agonists is usually given 30 mg of methadone initially and another 10 mg in 3-8 hours if necessary. The total dose on the first day should not exceed 40 mg unless it is previously documented that this total dose does not suppress withdrawal symptoms. If the patient has not been taking opiate agonists in the few days prior to initiation of methadone therapy or if he is a light user of opiate agonists he should receive one-half the above-mentioned dosage.
A common induction process can be summarized in the table below:

Day	Time (h)	Dose(mg)	Remarks
1	0	20-30	Usual initial dose.
1	3+	5-10	Persistent objective and subjective abstinence syndrome.
1	6+	5-10	Persistent objective and subjective abstinence syndrome.
2	0	5, 10 or 20 more than the	Adjustment rate increased or decreased on the basis of

		previous total daily dose	response to the total dose of the previous day.
2	3+	5-10	Persistent objective and subjective abstinence syndrome
3	0	5, 10 or 20 more than the previous total daily dose	Adjustment rate increased or decreased on the basis of response to the total dose of the previous day.
4-10	0	5, 10 or 20 more than the previous total daily dose	May be repeated on a daily basis with continuous stabilization evaluation and dosage adjustment, until a predetermined ceiling is reached.

Stabilization of maintenance dosage usually occurs at 40-120 mg daily, although higher dosage is sometimes required. Maintenance dosage requirements should be reviewed regularly and reduced as indicated. All patients in a maintenance program should be given careful consideration for discontinuance of methadone therapy, especially after reaching a dosage of 10-20 mg daily.

Pediatric population
Not recommended for children under 18 years.

Patients with renal failure
Depending on the severity of renal impairment in patients with renal failure the interval until the next dose of methadone should be increased.

Patients with liver impairment
Methadone maintenance doses need not be changed in patients with stable chronic liver disease, specifically cirrhosis. Abrupt changes in hepatic status might result in substantial alterations in methadone disposition requiring dosage adjustments.

Elderly patients
Methadone has a long half-life and accumulation may occur with repeated doses, especially in elderly or debilitated patients. Geriatric patients should receive the lowest possible dose of methadone.

4.3 Contraindications

Known hypersensitivity to hydroxybenzoates or methadone.
Respiratory depression, obstructive airway disease. Use during an acute asthma attack is not recommended.
Patients dependent on non-opioid drugs (detoxification and maintenance)
Concurrent administration with MAO inhibitors or within two weeks of discontinuation of treatment with them.
Use of methadone during labour is not recommended; the prolonged duration of action increases the risk of neonatal depression.
Raised intracranial pressure or head injury.
Phaeochromocytoma.
Risk of paralytic ileus (including drug induced gastrointestinal hypotonia).

4.4 Special warnings and special precautions for use

Caution should be exercised in patients with hepatic dysfunction or renal dysfunction.
In the case of the elderly or ill patients repeated doses should only be given with extreme caution.

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Addiction/tolerance/dependence
Methadone is a substance of addiction. It has a long half-life and can therefore accumulate. A single dose which will relieve symptoms may, if repeated on a daily basis, lead to accumulation and possible death.
Tolerance and dependence may occur as with morphine.
Methadone can produce drowsiness and reduce consciousness although tolerance to these effects can occur after repeated use.
Withdrawal
Abrupt cessation of treatment can lead to withdrawal symptoms which, although similar to those with morphine, are less intense but more prolonged. Withdrawal of treatment should therefore be gradual.
Respiratory depression
Due to the slow accumulation of methadone in the tissues, respiratory depression may not be fully apparent for a week or two and may exacerbate asthma due to histamine release.
Use during an asthma attack is not recommended.
Hepatic disorders
Caution is required as methadone may precipitate porto-systemic encephalopathy in patients with severe liver damage.
Opioids including methadone may cause troublesome constipation, which is particularly dangerous in patients with severe hepatic impairment, and measures to avoid constipation should be initiated early.
Biliary tract disorders.

Further warnings

Babies born to mothers receiving methadone may suffer withdrawal symptoms.

Methadone should be used with great caution in patients with acute alcoholism, convulsive disorders and head injuries.

Methadone has the potential to increase intracranial pressure especially where it is already raised.

Methadone should be used with caution in patients with hypothyroidism, adrenocortical insufficiency, prostatic hyperplasia, hypotension, shock, inflammatory or obstructive bowel disorders or myasthenia gravis.

Cases of QT interval prolongation and *torsades de pointes* have been reported during treatment with methadone, particularly at high doses (>100 mg/day). Methadone should be administered with caution to patients at risk for development of prolonged QT interval, e.g. in case of:
- history of cardiac conduction abnormalities,
- advanced heart disease or ischaemic heart disease,
- liver disease,
- family history of sudden death,
- electrolyte abnormalities, i.e. hypokalaemia, hypomagnesaemia,
- concomitant treatment with substances that have a potential for QT-prolongation,
- concomitant treatment with substances which may cause electrolyte abnormalities,
- concomitant treatment with cytochrome P450 CYP3A4 inhibitors (see section 4.5).

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In patients with recognised risk factors for QT-prolongation, or in case of concomitant treatment with substances that have a potential for QT-prolongation, ECG monitoring is recommended prior to methadone treatment, with a further ECG test at dose stabilisation.
ECG monitoring is recommended, in patients without recognised risk factors for QT-prolongation, before dose titration above 100 mg/day and at seven days after titration.

Caution should be exercised in patients who are concurrently taking central nervous system (CNS) depressants.

Excipients
This medicinal product contains sorbitol. 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

MAO inhibitors
The concurrent use of MAO inhibitors is contraindicated (see section 4.3) as they may prolong and enhance the respiratory depressant effects of methadone.
CNS depressants
Anaesthetics, hypnotics, anxiolytics, sedatives, barbiturates, phenothiazines, some other major tranquillizers and tricyclic antidepressants may increase the general depressant effects of methadone when used concomitantly (see section 4.4).
Antipsychotics may enhance the sedative effects and hypotensive effects of methadone.
Methadone may increase desimipramine levels by up to a factor of two.
There are reports that antidepressants (e.g. fluvoxamine and fluoxetine) may increase serum levels of methadone.
Alcohol may enhance the sedative and hypotensive effects of methadone and increase respiratory depression.
Histamine H_2 antagonists
Histamine H_2 antagonists such as cimetidine can reduce the protein binding of methadone resulting in increased opiate action.
Antibacterials
Rifampicin: Reduced plasma levels and increased urinary excretion of methadone can occur with concurrent administration of rifampicin. Adjustment of the dose of methadone may be necessary.
Ciprofloxacin: Plasma levels of methadone may increase with concurrent administration of ciprofloxacin due to inhibition of CYP 1A2 and CYP 3A4. Reduced serum concentrations of ciprofloxacin may occur. Concomitant use may lead to sedation, confusion and respiratory depression.
Erythromycin: Theoretically this may increase methadone levels due to decreased methadone metabolism.
Fluconazole and ketoconazole: May raise methadone levels, due to decreased methadone metabolism.
Anticonvulsants such as phenytoin, phenobarbital, carbamazepine and primidone
Anticonvulsants induce methadone metabolism with the risk of precipitating withdrawal syndrome. Adjustment of the dose of methadone should be considered.
pH of urine
Substances that acidify or alkalinise the urine may have an effect on clearance of methadone as it is increased at acidic pH and decreased at alkaline pH.
Opioid agonist analgesics

Additive CNS depression, respiratory depression and hypotension.

Opioid antagonists

Naloxone and naltrexone antagonises the analgesic, CNS and respiratory depressant effects of methadone and can rapidly precipitate withdrawal symptoms (see section 4.9). Similarly buprenorphine and pentazocine may precipitate withdrawal symptoms.

Antiretroviral agents such as nevirapine, efavirenz, nelfinavir, ritonavir

Based on the known metabolism of methadone, these agents may decrease plasma concentrations of methadone by increasing its hepatic metabolism. Methadone may increase the plasma concentration of zidovudine. Narcotic withdrawal syndrome has been reported in patients treated with some retroviral agents and methadone concomitantly. Methadone maintained patients beginning antiretroviral therapy should be monitored for evidence of withdrawal and the methadone dose should be adjusted accordingly.

Cyclizine and other sedating antihistamines

May have additive psychoactive effects; antimuscarinic effects at high doses.

Other Drugs

Methadone may have an effect on other drugs as a consequence of reduced gastro-intestinal motility.

Pregnancy Tests

Methadone may interfere with the urine testing for pregnancy.

Cytochrome P450 3A4 inhibitors

Methadone clearance is decreased when co-administered with drugs which inhibit CYP3A4 activity, such as some anti-HIV agents, macrolide antibiotics, cimetidine and azole antifungal agents (since the metabolism of methadone is mediated by the CYP3A4 isoenzyme).

St. John's Wort

May lower plasma concentrations of methadone.

Grapefruit Juice

There are several anecdotal reports of raised methadone levels due to decreased methadone metabolism.

Drugs affecting gastric emptying

Domperidone and metoclopramide may increase the speed of onset but not the extent of methadone absorption by reversing the delayed gastric emptying associated with opioids. Conversely, methadone may antagonise the effect of domperidone/metoclopramide on gastro-intestinal activity.

Antiarrhythmics

Methadone delays the absorption of mexiletine.

Methadone and QT interval prolongation

In patients taking drugs affecting cardiac conduction, or drugs which may affect electrolyte balance there is a risk of cardiac events when methadone is taken concurrently. Please refer to Section 4.4.

4.6 Fertility, pregnancy and lactation

Pregnancy

There is no evidence of safety in human pregnancy. A careful risk/benefit assessment should be made before administration to pregnant women because of possible adverse effects on the foetus and neonate including respiratory depression, low birth weight, neonatal withdrawal syndrome and increased rate of stillbirths. However, methadone has not been associated with congenital malformations.

It may be necessary to increase the dose of methadone if withdrawal symptoms develop. Increased clearance and reduced plasma levels have been reported during pregnancy.

During labour there is a risk of gastric stasis and inhalation pneumonia in the mother and foetal distress. Methadone should not be used during labour (see 4.3 Contraindications).
Lactation
Methadone is excreted in breast milk. Specialist care for obstetric and paediatric staff with experience in such management is required. If breast feeding is considered, the dose of methadone should be as low as possible and the infant monitored to avoid sedation. Breast-fed infants may develop physical dependence and exhibit withdrawal symptoms.

4.7 Effects on ability to drive and use machines

Methadone has a influence on the ability to drive and use machines, during and after treatment, as it may cause drowsiness and reduce alertness. Patient should drive and use machines if recommended by the physician.

4.8 Undesirable effects

The adverse effects of methadone are generally the same as with other opioids, most commonly nausea and vomiting.
The most serious adverse effect of methadone is respiratory depression, which may emerge during the stabilisation phase. Apnoea, shock and cardiac arrest have occurred.

Adverse reactions listed below are classified according to frequency and system organ class. These reactions are more frequently observed in non-opioid-tolerant individuals. Frequency groupings are defined according to the following convention: very common (≥ 1/10), common (≥ f /100 to < 1/10), uncommon (≥ 1/1.000 to < 1/100), rare (≥ 1/10.000 to < 1/1,000), very rare (< 1/10.000), not known (cannot be estimated from the available data).

System organ class (MedDRA)	Frequency	Adverse event
Blood and lymphatic system disorders	Not known	Reversible thrombocytopenia has been reported in opioid-dependent patients with chronic hepatitis.
Endocrine disorders	Not known	Raised prolactin levels with long-term administration
Metabolism and nutrition disorders	Common	Fluid retention
	Not known	Anorexia, hypokalaemia, hypomagnesaemia
Psychiatric disorders	Common	Euphoria, hallucinations
	Uncommon	Dysphoria, dependence, agitation, insomnia, disorientation, reduced libido
Nervous system disorders	Common	Sedation
	Uncommon	Headache, syncope
Eye disorders	Common	Blurred vision, miosis, dry eyes
Ear and labyrinth disorders	Common	Vertigo
	Not known	Hearing loss
Cardiac disorders	Rare	Bradycardia, palpitations, cases of prolonged QT interval and *torsade de pointes* have been reported, especially with high doses of

		methadone.
Vascular disorders	Uncommon	Facial flush, hypotension
	Rare	Shock
Respiratory, thoracic and mediastinal disorders	Uncommon	Pulmonary oedema, exacerbation of asthma, dry nose, respiratory depression particularly with large doses.
	Rare	Respiratory arrest
Gastrointestinal disorders	Very common	Nausea, vomiting
	Common	Constipation
	Uncommon	Xerostomia, glossitis
	Rare	Intestinal hypomotility (ileus)
Hepatobiliary disorders	Uncommon	Bile duct dyskinesia
Skin and subcutaneous tissue disorders	Common	Transient rash, sweating
	Uncommon	Pruritus, urticaria, other rash and in very uncommon cases bleeding urticara
Renal and urinary disorders	Uncommon	Urinary retention, anti-diuretic effect
Reproductive system and breast disorders	Uncommon	Reduced potency, galactorrhoea, dysmenorrhea and amenorrhoea
General disorders and administration site condition	Common	Fatigue, drosiness
	Uncommon	Oedema of the lower extremities, asthenia, oedema, hypothermia
Investigations	Common	Weight increase

In long term use of methadone, as for maintenance treatment, the undesirable effects diminish successively and progressively during a period of several weeks however, constipation and perspiration often remain.

4.9 Overdose

Symptoms
Serious overdose is characterised by respiratory depression, extreme somnolence progressing to stupor or coma, maximally constricted pupils, skeletal muscle flaccidity, cold and clammy skin and sometimes bradycardia and hypotension. In severe overdose, particularly by the intravenous route, apnoea, circulatory collapse, cardiac arrest and death may occur.
Treatment
A patent airway and assisted or controlled ventilation must be assured. Narcotic antagonists may be required, but it should be remembered that methadone is a long-acting depressant (36 to 48 hours), whereas antagonists act for 1 to 3 hours, so that treatment with the latter must be repeated as needed. An antagonist should not be administered, however, in the absence of clinically significant respiratory or cardiovascular depression. The administration of naloxone is advised. Oxygen, intravenous fluids, vasopressors and other supportive measures should be employed as indicated.

In a person physically dependent on narcotics, administration of the usual dose of a narcotic antagonist will precipitate an acute withdrawal syndrome; use of the antagonist in such a person should be avoided if possible but if it must be used to treat serious respiratory depression if should be administered with great care.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Drug used in opioid dependence
ATC code: N07BC02

Methadone is a strong opioid agonist with actions predominantly at the μ receptor. The analgesic activity of the racemate is almost entirely due to the *l*-isomer, which is at least 10 times 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 has some agonist actions at the κ and δ opiate receptors.
These actions result in analgesia, depression of respiration, suppression of cough, nausea and vomiting (*via* an effect of the chemoreceptor trigger zone) and constipation. An effect on the nucleus of the oculomotor nerve, and perhaps on opioid receptors in the pupillary muscles, causes pupillary constriction.
All these effects are reversible by naloxone with a pA_2 value similar to its anti-antagonism of morphine. Like many basic substances, methadone enters mast cells and releases histamine by a non-immunological mechanism. It causes a dependence syndrome of the morphine type.

5.2 Pharmacokinetic properties

Absorption
Methadone is one of the more lipid-soluble opioids and is well absorbed from the gastrointestinal tract, but undergoes fairly extensive first-pass metabolism. The bioavailability is above 80%. Steady state concentrations are reached within 5-7 days.
Distribution
Methadone is bound to albumin and other plasma proteins and to tissue proteins (probably lipoproteins), the concentrations in the lung, liver and kidneys being much higher than in blood. The pharmacokinetics of methadone is unusual, in that there is extensive binding to tissue proteins and fairly slow transfer between some parts of this tissue reservoir and the plasma. Methadone is secreted in sweat and found in saliva, breast milk and in the cord blood.
Metabolism
The metabolism of methadone is catalysed primarily by CYP3A4, but CYP2D6 and CYP2B6 are also involved, to a smaller extent. Metabolism is mainly *N*-demethylation, which produces the most important metabolites: 2-ethylidine, 1,5-dimethyl-3,3-diphenylpyrrolidine (EDDP) and 2-ethyl-5-methyl-3,3-diphenyl-1-pyrrolidine (EMDP).
Elimination
The half-life after a single oral dose is 12-18 (mean 15) hours, partly reflecting distribution into tissue stores, as well as metabolic and renal clearance. With regular doses, the tissue reservoir is already partly filled and so the half-life is extended to 13-47 hours (mean 25) hours reflecting only clearance.
Methadone and its metabolites are excreted to varying degree in the feces and urine. Excretion of methadone is markedly enhanced by the acidification of the urine.

Special populations
There are no significant differences in the pharmacokinetics between men and women. The clearance of methadone is decreased only to some extent in die elderly (>65 years).

5.3 Preclinical Safety Data

Methadone at high doses caused birth abnormalities in marmots, hamsters and mice, in which most reports were of exencephaly and defects in the central nervous system. Rachischisis in the cervical region was found occasionally in mice. Non-closure of the neural tube was found in chicken embryos. Methadone was not teratogenic in rats and rabbits. Also a reduced number of young was found in rats and increased mortality, growth retardation, neurological behavioural effects and reduced brain weight were found in the pups. Reduced ossification of the digits, sternum and skull was found in mice and a smaller number of fetuses per litter. No carcinogenicity studies have been carried out.

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

sorbitol, liquid, non-crystallising (E 420),
glycerol (E 422),
sodium benzoate (E 211),
citric acid monohydrate (E 330),
water, purified.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

4 (four) years.
The medicine may be used within 90 days from the initial opening, when stored in the original package to protect from light.

6.4 Special precautions for storage

This medicinal product does not require special storage conditions.

6.5 Nature and contents of container

Bottle containing 100 ml oral solution with plastic cap and plastic graduated pipette.
Bottle containing 1000 ml oral solution with plastic cap.

6.6 Instructions for use/handling

Peroral use only.

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Due to the risk for abuse (injecting methadone) it is recommended that in patients on maintenance treatment with methadone each dose is diluted with water (or other suitable liquid, for example, orange juice).

7. MARKETING AUTHORISATION HOLDER

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8. MARKETING AUTHORISATION NUMBER

9. DATE OF FIRST AUTHORISATION/ RENEWAL OF AUTHORISATION

10. DATE OF REVISION OF THE TEXT

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