Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Methadone Hydrochloride 5 mg tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 5 mg of methadone hydrochloride.
Excipient with known effect: each tablet contains 79.2 mg lactose monohydrate.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet

White or almost white, round, flat uncoated tablets of 7 mm, imprinted with “M5” on one side and concave with a score line on the other side. The score line is not intended for breaking the tablet.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Severe pain where morphine may be a reasonable alternative, such as severe cancer pain.

4.2 Posology and method of administration

Posology

Adults:
Usual adult dose 5-10 mg.
Owing to its long plasma half-life caution with repeated dosage should be observed in the very ill or elderly. The usual initial dose should be 5-10 mg, 6-8 hourly, later adjusted to the degree of pain relief obtained.

Paediatric population:
Not suitable

Elderly:
Use caution with repeated dosage in elderly and ill patients.

Method of administration
For oral administration only. The product is for oral use only and must not be injected.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Respiratory depression, obstructive airways disease.
- In cases of acute alcoholism,
- Head injury or raised intracranial pressure.
- It is not recommended during an asthma attack or where there is a risk of paralytic ileus.
- Concurrent administration with monoamine oxidase inhibitors (including moclobemide), or within 2 weeks of discontinuation of treatment with them. Concurrent use of other central nervous system depressants.
- Obstetric use is not recommended, because in labour the prolonged duration of action increases the risk of neonatal respiratory depression.

Methadone is not suitable for children (see section 4.2 and 5.2). Babies born to mothers receiving methadone may suffer withdrawal symptoms.

- Individuals with QT prolongation, including congenital long QT syndrome (see section 4.4)
- As with all opioid analgesics, this product should not be administered to patients with severe hepatic impairment as it may precipitate Porto- systemic Encephalopathy in patients with severe liver damage.
- As with other opioid drugs, methadone may cause constipation which is particularly dangerous in patients with severe hepatic impairment and measures to avoid constipation should be initiated early.

4.4 Special warnings and precautions for use

Tolerance and dependence of the morphine type may occur, though it is said that methadone has a greater respiratory depressive effect and a lesser sedative effect than an equianalgesic dose of morphine. Toxic doses are highly variable, regular usage giving tolerance. Pulmonary oedema is a frequent corollary of overdosage whilst the dose-related histamine-releasing property of methadone may account for at least some of the urticaria and pruritic associated with methadone administration. Methadone may lead to an increase in intracranial pressure.

Adverse effects occurring more rarely in patients being treated for opioid addiction are as follows:

(a) A number of heroin patients have been reported to die within a few days of starting a methadone maintenance programme. Evidence of chronic persistent hepatitis was detected in ten heroin patients, who died within 2-6 days of starting methadone treatment. The mean prescribed dose at the time of death was about 60mg. It has been suggested that these sudden deaths may have arisen as a result of accumulation of methadone over several days resulting in death from complications such as cardiac arrhythmias or cardiovascular collapse as methadone, like dextropropoxyphene, has membrane stabilising activity and can block nerve conduction.

In view of the possibility of reduced clearance and raised plasma levels it is recommended that liver function tests and urine tests be carried out prior to maintenance and that lower starting doses of methadone be used.

(b) Evidence of hypoadrenalism has been found in chronic methadone patients. Findings consistent with both deficient ACTH production and subsequent secondary hypoadrenalism and methadone induced primary adrenal cortical hypofunction have been reported.

(c) Choreic movements involving the upper limbs, torso and speech mechanisms have been reported in a 25-year-old man receiving methadone hydrochloride maintenance therapy (45-60 mg/day) for 2 years. Discontinuation of methadone resulted in complete alleviation of the abnormal movements with no recurrence during the subsequent eight months.

(d) The function of the secondary sex organs was found to be markedly impaired in 29 male participants in a methadone maintenance programme. The ejaculate volume and seminal vesicular and prostatic secretions in subjects maintained on methadone (mean daily dose 66.9 mg) were reduced by over 50% compared to 16 heroin patients and 43 opioid-free controls. Serum testosterone levels were also approximately 43% lower in those on methadone. Whilst the sperm counts of the

methadone users were more than twice the control level, reflecting a lack of sperm dilution by secondary sex organ secretion, the sperm motility of these subjects was markedly lower than normal.

Methadone should be given with caution to patients with asthma, convulsive disorders, depressed respiratory reserve, hypotension, hypothyroidism or prostatic hypertrophy. In cases of hepatic or renal impairment the use of methadone should be avoided or given in reduced doses.

Cases of QT interval prolongation and torsades de pointes have been reported during treatment with methadone, particularly at high doses (> 100 mg/d). Methadone should be administered with caution to patients at risk for the development of prolonged QT interval, e.g. in case of:

- history of cardiac conduction abnormalities,
- advanced heart disease or ischaemic heart disease, known history of QT prolongation
- liver disease,
- family history of sudden death,
- electrolyte abnormalities, i.e. hypokalaemia, hypomagnesaemia
- concomitant treatment with drugs that have a potential for QT-prolongation,
- concomitant treatment with drugs which may cause electrolyte abnormalities,
- concomitant treatment with cytochrome P450 CYP3A4 inhibitors (see section 4.5).

In patients with recognised risk factors for QT-prolongation, or in case of concomitant treatment with drugs 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 100mg/d and at seven days after titration.

Paediatric population
Children are more sensitive than adults and intoxication may follow a low dose intake of methadone. To avoid such intoxication following dose administration by mistake, methadone should be kept in a safe place out of reach by children when located at home.

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 interactions

Pharmacokinetic interactions

P-glycoprotein inhibitors: Methadone is a substrate of p-glycoprotein; all medicinal products that inhibit P-glycoprotein (e.g. qunidine, verapamil, ciclosporin), may therefore raise the serum concentration of methadone. The pharmacodynamic effect of methadone may also increase because of increased blood brain barrier passage.

CYP3A4-enzyme inducers: Methadone is a substrate of CYP3A4 (see section 5.2). By induction of CYP3A4, clearance of methadone will increase and the plasma levels decrease. Inducers of this enzyme (barbiturates, carbamazepine, phenytoin, nevirapine, rifampicin, efavirenz, amprenavir, spirononlactone, dexamethasone, Hypericum perforatum (St John's Wort), may induce hepatic metabolism. For instance, after three weeks treatment with 600 mg efavirenz daily, the mean maximal plasma concentration and AUC decreased by 48 % and 57 % respectively, in patients treated with methadone (35-100 mg daily). The consequences of enzyme induction are more marked if the inducer is administered after treatment with methadone has begun. Abstinence symptoms have been reported following such interactions and hence, it may be necessary to increase the methadone dose. If treatment with a CYP3A4 inducer is interrupted, the methadone dose should be reduced.

CYP3A4-enzyme inhibitors: Methadone is a substrate of CYP3A4 (see section 5.2). By inhibition of CYP3A4 clearance of methadone is lowered. Concomitant administration of CYP3A4 inhibitors (e.g. cannabinoids, clarithromycin, delavirdine, erythromycin, fluconazole, grapefruit juice, itraconazole, ketoconazole, fluoxetine, fluvoxamine, nefazodone and telithromycin) may result in increased plasma concentrations of methadone. A 40-100 % increase of the quote between the serum levels and

the methadone dose has been shown with concomitant fluvoxamine treatment. If these medicinal products are prescribed to patients on methadone maintenance treatment, one should be aware of the risk of overdose.

Products that affect the acidity of the urine: Methadone is a weak base. Acidifiers of the urine (such as ammonium chloride and ascorbic acid) may increase the renal clearance of methadone. Patients that are treated with methadone are recommended to avoid products containing ammonium chloride.

Concomitant HIV infection treatment: Some protease inhibitors (amprenavir, nelfinavir, lopinavir/ritonavir and ritonavir/saquinavir) seem to decrease the serum levels of methadone. When ritonavir is administered alone, a twofold AUC of methadone has been observed. The plasma levels of zidovudin (a nucleoside analogue) increase with methadone use after both oral and intravenous administration of zidovudin. This is more noticeable after oral than after intravenous use of zidovudin. These observations are likely caused by inhibition of zidovudine glucuronidation, and therefore, decreased clearance of zidovudin. During treatment with methadone, patients must be carefully monitored for signs of toxicity caused by zidovudine, why it may be necessary to reduce the dose of
zidovudin. Because of mutual interactions between zidovudin and methadone (zidovudine is a CYP3A4 inducer), typical opioid abstinence symptoms may develop during concomitant use (headache, myalgia, fatigue and irritability).

Didanosine and stavudine: Methadone delays the absorption and increases the first pass metabolism of stavudine and didanosine which results in a decreased bioavailability of stavudine and didanosine.
Methadone may double the serum levels of desipramine.

Pharmacodynamic interactions

Opioid antagonists: Naloxone and Naltrexone counteracts the effects of methadone and induces abstinence.

CNS depressants: Medicinal products with a sedative effect on the central nervous system may result in 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. With methadone treatment, the slowly eliminated substance methadone, give rise to a slow tolerance development and every 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 with careful observation.

Peristalsis inhibition: Concomitant use of methadone and peristalsis inhibiting medicinal products (loperamide and diphenoxylate) may result in severe obstipation and increase the CNS depressant effects. Opioid analgesics, in combination with antimuscarinics, may result in severe obstipation or paralytic ileus, especially in longterm use.

QT-prolongation: Methadone should not be combined with medicinal products that may prolong the QT interval such as antiarrhytmics (sotalol, amiodarone, and flecainid), antipsychotics (thioridazine, haloperidol, sertindo, and phenotiazines), antidepressants (paroxetine, sertraline) or antibiotics (erythromycin, clarithromycin).

MAO-inhibitors: Concomitant administration of MAO-inhibitors may result in reinforced CNS-inhibition, serious hypotonia and or apnoea. Methadone should not be combined with MAO-inhibitors and two weeks after such treatment (see section4.3).

Opioid analgesics delay gastric emptying, thereby invalidating test results. Delivery of technetium Tc 99m disofenin to the small bowel may be prevented and plasma amylase and plasma lipase activity may increase because opioid analgesics may cause constriction of the sphincter of Oddi and increased biliary tract pressure; these actions result in delayed visualization and thus resemble obstruction of the common bile duct.

The diagnostic utility of determinations of these enzymes may be compromised for up to 24 hours after the medication has been given. Cerebrospinal fluid pressure (CSF) may be increased; effect is secondary to respiratory depression –induced carbon dioxide retention.

Ciprofloxacin may increase levels of methadone by inhibiting its metabolism. With anti-arrhythmics there may be a delayed absorption of mexiletine.

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.

4.6 Fertility, pregnancy and lactation

Pregnancy:
Limited data on the use of methadone in pregnancy in humans show no elevated risk of congenital abnormalities. Withdrawal symptoms / respiratory depression might occur in neonates of mothers that were treated with methadone chronically during pregnancy. Data from animal studies have shown reproduction toxicity (see section 5.3). It is generally advisable not to detoxify the patient, especially after the 20th week of pregnancy, but to administer maintenance treatment with methadone. The use of Methadone oral solution just before and during birth is advised against because of the risk of neonatal respiratory depression.

Breastfeeding:
Methadone is excreted in breast milk and the average milk/plasma ratio is 0.8. Breast feeding may be given on doses of up to 20mg per day. At higher doses, the benefits of breast feeding must be weighed against the possible adverse effects on the infant.

Fertility:
No pre-clinical nor clinical trial data are available on the effects of methadone on human fertility.

4.7 Effects on ability to drive and use machines

Methadone will affect the psychomotor functions until the patient has been stabilised at a suitable level. The patient should therefore not drive or use machines until stabilisation has been achieved and there have been no symptoms of abuse for the last six months. When, driving and use of machines can be resumed, is largely dependent on the individual patient and must be determined by the physician. For further information see the national guidelines for methadone treatment. This medicine can impair cognitive function and can affect a patient's ability to drive safely. This class of medicine is in the list of drugs included in regulations under 5a of the Road Traffic Act 1988. When prescribing this medicine, patients should be told:

- The medicine is likely to affect your ability to drive
- Do not drive until you know how the medicine affects you
- It is an offence to drive while under the influence of this medicine
- However, you would not be committing an offence (called 'statutory defence') if:

- The medicine has been prescribed to treat a medical or dental problem and
- You have taken it according to the instructions given by the prescriber and in the information provided with the medicine and
- It was not affecting your ability to drive safely.

4.8 Undesirable effects

The undesirable effects of methadone treatment are in general the same as when treated with other opioids. The most common side effects are nausea and vomiting that is observed in approximately 20 % of the patients that go through methadone outpatient treatment, where the medicinal control is often unsatisfactory.

The most serious side effect of methadone is respiratory depression, which may emerge during the stabilization phase. Apnoea, shock and cardiac arrest have occurred.

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

System organ class (MedDRA)	Frequency	Adverse event
Blood and lymphatic system disorders	Not known	Reversible thrombocytopenia has been reported in opioid dependent patients with chronic hepatitis.
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
Ear and labyrinth disorders	Common	Vertigo
Cardiac disorders	Rare	Bradycardia, palpitations, cases of prolonged QT interval and torsade depointes have been reported, especially with high doses of methadone.
Vascular disorders	Uncommon	Facial flush, hypotension

Respiratory, thoracic and mediastinal disorders	Uncommon	Pulmonary oedema, respiratory depression particularly with large doses.
Gastrointestinal disorders	Very common	Nausea, vomiting
	Common	Constipation
	Uncommon	Xerostomia, glossitis
Hepatobiliary disorders	Uncommon	Bile duct dyskinesia
Skin and subcutaneous tissue disorders	Common	Transient rash, sweating
	Uncommon	Pruritis, urticaria, other rash and in very uncommon cases bleeding urticaria.
Endocrine disorders	Not known	Hyperprolactinaemia
Renal and urinary disorders	Uncommon	Urinary retention, antidiuretic effect
Reproductive system and breast Disorders	Uncommon	Reduced potency, galactorrhoea, dysmenorrhoea and amenorrhoea
General disorders and administration site conditions	Common	Fatigue
	Uncommon	Oedema of the lower extremities, asthenia, oedema,
Investigations	Common	Weight increase
Ear and labyrinth disorders	Common	Vertigo
Eye disorders	Common	Sedation
Nervous system disorders	Common	Blurred vision, miosis
	Uncommon	Headache, syncope
Skin and subcutaneous tissue disorders	Common	Transient rash, sweating
	Uncommon	Pruritus, urticaria, other rash and in very uncommon cases bleeding urticaria.
General disorders and administration site conditions	Common	Fatigue

	Uncommon	Oedema of the lower extremities, asthenia, oedema
Hepatobiliary disorders	Uncommon	Bile duct dyskinesia
Vascular disorders	Uncommon	Facial flush, hypotension
Cardiac disorders	Rare	Bradycardia, palpitations, cases of prolonged QT intervals and "torsade de pointes" have been reported in treatment with methadone, especially with high doses.
Reproductive system and breast disorders	Uncommon	Reduced 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 HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; E-mail: medsafety@hpra.ie.

4.9 Overdose

The symptoms and signs of overdosage and toxicity of methadone are essentially those for morphine, though respiratory depression may be more profound and prolonged than for an equivalent dose of morphine. Severe overdose is characterised by respiratory failure, extreme drowsiness that develops into stupor or coma, maximum pupillary constriction, skeletal-muscle flaccidity, cold and clammy skin and occasionally bradycardia and hypotension.
Apnoea, cardiovascular failure, cardiac arrest and death may occur in serious cases of overdose, especially in intravenous administration.

Treatment is supportive and use of an opioid antagonist such as naloxone, malorphine or levallorphan should be limited to those patients with demonstrated respiratory or cardiovascular depression due to methadone.

Naloxone is the preferred antagonist as there is less likelihood of further respiratory depression from the effects of the opioid antagonist. Use of an opioid antagonist may need to be continued for up to 48 hours due to the duration of action of methadone, and for this reason respiratory and cardiovascular monitoring is mandatory. Dialysis, CNS stimulation and respiratory stimulants are contraindicated. Acidification of the urine will increase the renal clearance of the drug.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Drugs used in opioid dependence

ATC code: N07BC02

Methadone is an opioid analgesic in the same manner of morphine and like morphine is highly addictive drug in its own right. It has a less sedative effect than morphine. It acts on the CNS system and smooth muscle. This action is caused by the response of structurally and sterically specific opiate receptor sites in the brain, spinal cord and nervous system.

Methadone is an 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 σ opiate receptors. These actions result in analgesia, depression of respiration, suppression of cough, nausea and vomiting (via an effect on the chemoreceptor trigger zone) and constipation. An effect on the nucleus of the automotor nerve and perhaps on opioid receptors in the pupillary muscles causes pupillary constriction. All these effects are reversible by naloxone with a pA2 value similar to its antagonism of Morphine. Like many basic drugs, Methadone enters mast cells and releases histamine by a nonimmunological mechanism. It causes a dependence syndrome of the Morphine type.

5.2 Pharmacokinetic properties

Absorption
Methadone is rapidly absorbed following oral administration, but undergoes considerable first-pass metabolism. The bioavailability is above 80 %. Steady state concentrations are reached within 5-7 days.

Distribution
Distribution volume: 5 L/kg. Protein binding: up to 90 %, but with great individual differences. Methadone binds mainly to alpha1-glycoprotein acid, but also to albumin and other plasma and tissue proteins. Plasma: the full blood ratio is around 1:3. It is distributed to tissue with higher concentrations in the liver, lungs and kidneys than in the blood.

Metabolism
Catalysed primarily by CYP3A4, but CYP2D6 and CYP2B6 are also involved, but to a smaller extent.
Metabolism is mainly N-demethylisation, 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), which are both inactive. Hydroxylation to methanol succeeded by Ndemethylisation to normethadol also occurs to some 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: 13-55hours. Plasma clearance is around 2 ml/min/kg. About 20-60 % of the dose is eliminated in urine over 96 hours (about 33 % in unmodified form, about 43 % as EDDP and about 5-10% as EMDP). The ratio between EDDP and unmodified methadone is usually much higher in urine in patients receiving methadone treatment compared to normal overdoses. Elimination of unmodified methadone in urine is pHdependent and increases with increasing acidity of the urine. About 30 % of the dose is eliminated in faeces, but this percentage will normally be reduced at higher doses. About 75 % of overall elimination is unconjugated.
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 elderly (>65 years). Because of increased exposure, caution is advised in the treatment of patients with renal and hepatic impairment (see section 4.4).

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. 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

Lactose monohydrate
Maize starch
Povidone K25
Silica colloidal anhydrous
Talc

Magnesium stearate

6.2 Incompatibilities

None known.

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

28, 30 or 50 tablets in clear, colourless PVC/PVDC//Al blisters in a carton box with leaflet.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Ascot Laboratories (Ireland) Limited
12 Merrion Square
Dublin 2
Ireland

8 MARKETING AUTHORISATION NUMBER

PA23163/002/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 21st September 2018

10 DATE OF REVISION OF THE TEXT

February 2021