Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Pinadone 1 mg/ml Oral Solution

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 5 ml contains 5 mg methadone hydrochloride

Excipients with known effect
Each 5 ml contains:
5.0 mg benzoic acid
100 mg propylene glycol
150 micrograms sunset yellow (E110)
2.75 g liquid maltitol
Less than 1 mmol (23 mg) sodium

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Oral solution.
Clear, green, viscous, oral solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Pinadone is an opioid analgesic indicated for the relief of severe pain in conditions where morphine may be a reasonable alternative, such as severe cancer pain.

For use in the treatment of opioid drug addictions (as a narcotic abstinence syndrome suppressant), as substitution or maintenance therapy, within a broader treatment protocol/programme, accompanied by regular reviews and reassessment. This treatment must be supervised by specialist services.

4.2 Posology and method of administration

Posology

Adults

ANALGESIA

The usual initial dose is 5 to 10 mg methadone, for oral administration.

Since rigid adherence to a dosage schedule may provide inadequate analgesia, subsequent doses should be adjusted according to individual patient response. However, doses administered more frequently than six to eight hourly are liable to cause accumulation with increasing sedation and respiratory depression. In chronic use methadone should not be administered more than twice daily.

Pinadone 1 mg/ml Oral Solution may be used in combination with non-narcotic analgesics to provide additive analgesia.

OPIOID ADDICTION

Dosing and duration should be individualised based on a careful evaluation of subjective and objective patient data, bearing in mind clinical status, including hepatic or renal function of the patient.
A daily dose of 10 to 40 mg of methadone hydrochloride by mouth may be given initially. This may be increased as necessary by no more than 10 mg in one day, with a maximum weekly increase of 30 mg, up to a total daily dose of between 60 mg and 120 mg, until there are no signs of withdrawal or intoxication. After stabilisation, the dose of methadone is gradually increased until total withdrawal is achieved. Some treatment schedules for opioid dependence involve prolonged maintenance therapy with methadone where the daily dose is adjusted carefully for the individual.

Children and adolescents aged less than 18 years
Pinadone is not recommended for use in this age group, since documented clinical experience has been insufficient to establish a suitable dose regimen; furthermore, children are particularly sensitive to the respiratory and central nervous system depressant effects of methadone.

Elderly people
Pinadone has a long plasma half life which may lead to accumulation, particularly if renal function is impaired (see section 4.4 and secion 5.2).

In common with other opioids, methadone may cause confusion in this age group, therefore careful monitoring is advised (see section 4.4 and section 5.2).

Hepatic impairment
Particular care should be taken when Pinadone is to be used in patients with hepatic impairment as these patients metabolise methadone more slowly than normal patients. Where not contraindicated, Pinadone should be given at less than the normal recommended dose and the patient's response used as a guide to further dosage requirements (see section 4.3).

Renal impairment
Pinadone should be used with caution in patients with renal dysfunction; the dosage interval should be increased to a minimum of eight hourly when the glomerular filtration rate (GFR) is 10 to 50 ml/minute and to a minimum of 12-hourly when the GFR is below 10 ml/minute.

Cardiac repolarisation disorder
Methadone should be administered with caution to patients at risk of development of prolonged QT interval (see sections 4.3 and 4.4).

Method of administration

Oral administration only.

Treatment goals and discontinuation
Before initiating treatment with Pinadone, a treatment strategy including treatment duration and treatment goals should be agreed together with the patient in accordance with pain management guidelines. During treatment, there should be frequent contact between the physician and the patient to evaluate the need for continued treatment, consider discontinuation and to adjust dosages if needed. When a patient no longer requires therapy with methadone, it may be advisable to taper the dose gradually to prevent symptoms of withdrawal (see section 4.4). In absence of adequate pain control, the possibility of tolerance and progression of underlying disease should be considered (see section 4.4).

4.3 Contraindications

Pinadone is contra-indicated in patients:

- With a hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- With respiratory depression, especially in the presence of cyanosis and excessive bronchial secretions.
- During an attack of bronchial asthma.
- With acute alcoholism, head injury and raised intracranial pressure.
- Receiving monoamine oxidase inhibitors or with 14 days of stopping such treatment (see section 4.5).
- With ulcerative colitis, since it may precipitate toxic dilation or spasm of the colon.

- With severe hepatic impairment as it may precipitate hepatic encephalopathy (see section 4.2).
- With biliary and renal tract spasm.
- Use during labour is not recommended, the prolonged duration of action increases the risk of neonatal depression (see section 4.6).

4.4 Special warnings and precautions for use

Deaths due to cardiac arrhythmias and respiratory depression may occur, particularly in patients receiving methadone for analgesia during treatment initiation or conversion from other opioids.

Respiratory depression
Respiratory depression is the major hazard associated with methadone treatment. The peak depressive effects persist longer than peak analgesic effects, especially during the initial dosing period. Particular care should be taken during the dose initiation and adjustment period to minimise the risk of dose accumulation (see Section 4.2).
Due to the slow accumulation of methadone in the tissues, respiratory depression may not be fully apparent for a week or two. Asthma may be exacerbated due to histamine release. Concomitant treatment with other agents with CNS depressant activity is not advised due to the potential for CNS and respiratory depression (see also section 4.5 Interactions).

Risk from concomitant use of sedative medicines such as benzodiazepines or related drugs:
Concomitant use of Pinadone 1 mg/ml Oral Solution and sedative medicines such as benzodiazepines or related drugs may result in sedation, respiratory depression, coma and death. Because of these risks, concomitant prescribing with these sedative medicines should be reserved for patients for whom alternative treatment options are not possible. If a decision is made to prescribe Pinadone 1 mg/ml Oral Solution concomitantly with sedative medicines, the lowest effective dose should be used, and the duration of treatment should be as short as possible.
The patients should be followed closely for signs and symptoms of respiratory depression and sedation. In this respect, it is strongly recommended to inform patients and their caregivers to be aware of these symptoms (see section 4.5).

Cardiac arrhythmias
Cases of QT interval prolongation and Torsade 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 of development of prolonged QT interval, e.g. in cases of:

- Known history of QT prolongation
- Advanced heart disease
- Ischaemic heart disease and liver disease
- Concomitant treatment with drugs that have a potential for QT-prolongation
- Patients with hypokalaemia
- Patients with electrolyte imbalance or drugs likely to cause electrolyte imbalance
- Patients with a family history of sudden death
- Patients who are taking other potentially arrythmogenic drugs
- Drugs that inhibit the cytochrome P450 isoenzyme CYP3A4 (see section 4.5).

ECG monitoring is recommended before starting methadone treatment in these patients, with a further test at dose stabilisation. ECG monitoring is also recommended before and at seven days after dose titration above 100 mg daily in patients without recognised risk factors.

Opioid Use Disorder (abuse and dependence)

Methadone is an opioid analgesic and is highly addictive in its own right. 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.

As with other opioids, tolerance, physical, and/or psychological dependence may develop upon repeated administration of methadone.

When used for the treatment of pain, repeated use of Pinadone can lead to Opioid Use Disorder (OUD). A higher dose and longer duration of opioid treatment can increase the risk of developing OUD.

Before initiating treatment with Pinadone and during the treatment, treatment goals and a discontinuation plan should be agreed with the patient (see section 4.2). Before and during treatment the patient should also be informed about the risks and signs of OUD. If these signs occur, patients should be advised to contact their physician.

Abuse or intentional misuse of Pinadone may result in overdose and/or death.

The risk of developing Opioid Use Disorder is increased in patients with a personal or a family history (parents or siblings) of substance use disorders (including alcohol use disorder), in current tobacco users or in patients with a personal history of other mental health disorders (e.g., major depression, anxiety and personality disorders).

Patients will require monitoring for signs of drug-seeking behaviour (e.g., too early requests for refills). This includes the review of concomitant opioids and psycho-active drugs (like benzodiazepines). For patients with signs and symptoms of OUD, consultation with an addiction specialist should be considered.

Sleep-related breathing disorders

Opioids can cause sleep-related breathing disorders including central sleep apnoea (CSA) and sleep-related hypoxemia. Opioid use increases the risk of CSA in a dose-dependent fashion. In patients who present with CSA, consider decreasing the total opioid dosage.

Methadone can produce drowsiness and reduce consciousness although tolerance to these effects can occur after repeated use.

Discontinuation of therapy

Discontinuation of therapy with opioid analgesics should be carried out gradually in patients who may have developed physical dependence, to avoid precipitating withdrawal symptoms (see section 4.8).

Other

Methadone should be used with caution in the presence of the following:

- Hypothyroidism
- Adrenocortical insufficiency
- Hypopituitarism
- Prostatic hypertrophy
- Shock
- Hypotension
- Inflammatory or obstructive bowel disorders
- Myasthenia gravis

Extreme caution should be exercised when administering methadone to patients with phaeochromocytoma, since aggravated hypertension has been reported in association with diamorphine.

Serotonin syndrome

Serotonin syndrome (including altered mental status such as agitation, hallucinations or coma; autonomic instability such as tachycardia, labile blood pressure or hyperthermia; and neuromuscular abnormalities) such as hyperreflexia, incoordination or rigidity) has been reported in patients taking opioids, particularly with concomitant use of other serotonergic agents (including SSRIs, SNRIs, tricyclic antidepressants). The onset of symptoms generally occurs within several hours to few days of concomitant use but may occur later, particularly after dose increase. If serotonin syndrome is suspected, opioid treatment and/or the concomitant serotonergic drug should be discontinued. If concomitant treatment with opioids is clinically warranted, appropriate observation of the patient is advised (see section 4.5). Methadone is contraindicated in patients taking monoamine oxidase inhibitors (MAOIs) or within 14 days of stopping such treatment (see section 4.3).

Adrenal insufficiency

Opioid analgesics may cause reversible adrenal insufficiency requiring monitoring and glucocorticoid replacement therapy. Treatment with opioids may result in acute suppression of ACTH (adrenocorticotropic hormone) secretion, which may lead to a decrease in circulating level of cortisol and potentially to hypocortisolism.

Symptoms of adrenal insufficiency may include nausea, vomiting, loss of appetite, fatigue, weakness, dizziness or low blood pressure. If adrenal insufficiency is suspected, it should be confirmed with diagnostic testing as soon as possible. The patient should be treated with physiological replacement doses of corticosteroids and opioid should be withdrawn to allow adrenal function to recover.

Decreased sex hormonesand increased prolactin

Long-term use of opioid analgesics may be associated with decreased sex hormone levels and increased prolactin. Symptoms include decreased libido, impotence, amenorrhea or infertility.

Hypoglycaemia

Hypoglycaemia has been observed in the context of methadone overdose or dose escalation. Regular monitoring of blood sugar is recommended during dose escalation (see section 4.8 and section 4.9).

Grapefruit juice

Grapefruit juice increases the bioavailability of methadone (see section 4.5).
This product contains maltitol. Patients with rare hereditary problems of fructose intolerance should not take this medicine.

Sunset yellow (E110) may cause allergic reactions.

This medicine contains 5.0 mg benzoic acid in each 5 ml which is equivalent to 1 mg/ml.

This medicine contains 100 mg propylene glycol in 5 ml which is equivalent to 20 mg/ml.

This medicine contains less than 1 mmol sodium (23 mg) per 5 ml, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

Cytochrome P450 (CYP450) enzymes
Methadone is metabolised by various cytochrome P450 (CYP450) enzymes. Therefore, co-administration of drugs known to interfere with CYP450 enzymes may affect its clinical activity (see section 5.2).

Monamine oxidase inhibitors
Monoamine oxidase inhibitors (MAOIs) may prolong and enhance the respiratory depressant effects of methadone. Opioids and MAOIs used together may cause fatal hypotension and coma (see section 4.3).

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

Compounds which may increase/decrease the metabolism of methadone
Some compounds may increase the metabolism of methadone, e.g. rifampicin, phenytoin, carbamazepine, St John's Wort, and antiretroviral agents used in the treatment of HIV infection (particularly nevirapine, efavirenz and some protease inhibitors). This has the potential to result in withdrawal symptoms.

Some compounds may decrease the metabolism of methadone, e.g. fluconazole and some selective serotonin re-uptake inhibitors (SSRIs), particularly fluvoxamine. This may increase the likelihood of methadone toxicity.

Methadone clearance decreases in case of co-administration of methadone and drugs which inhibit CYP3A4 activity, such as some anti-HIV agents, macrolides antibiotics, cimetidine and azole antifungal agents (since the metabolism of methadone is mediated by the CYP3A4 isoenzyme).

QT prolongation
In addition to compounds that may decrease the metabolism of methadone, extreme caution is necessary when any drug known to have the potential to prolong the QT interval is prescribed in conjunction with methadone (see section 4.4). Interactions may occur with methadone and potentially arrhythmogenic agents such as class I and III antiarrhythmics, some neuroleptics and tricyclic antidepressants, and calcium channel blockers.

Caution should also be exercised when prescribing concomitant drugs capable of inducing electrolyte disturbances that may prolong the QT interval (hypomagnesaemia, hypokalaemia). These include diuretics, laxatives and in rare cases mineralocorticoid hormones.

Influence on other drugs
Methadone can also affect the metabolism of other drugs. Plasma concentrations of some drugs may be increased, e.g. nelfinavir, zidovudine, fluconazole and desipramine, whereas concentrations of others may be decreased, e.g. abacavir and amprenavir.

Ciprofloxacin
Concomitant use may lead to sedation, confusion and respiratory depression.

Depressant effects
The general depressant effects of methadone may be enhanced by other centrally-acting agents such as, alcohol, barbiturates, neuromuscular blocking agents, phenothiazines and tranquillisers. Some psychotropic drugs, however, may potentiate the analgesic effects of methadone (see section 4.4).

Sedative medicines such as benzodiazepines or related drugs:
The concomitant use of opioids with sedative medicines such as benzodiazepines or related drugs increases the risk of sedation, respiratory depression, coma and death because of additive CNS depressant effect. The dose and duration of concomitant use should be limited (see section 4.4).

Serotonergic drugs
Serotonergic syndrome may occur with concomitant administration of methadone with pethidine, monoamine oxidase (MAO) inhibitors and serotonin agents such as Selective Serotonin Re-uptake Inhibitor (SSRI), Serotonin Norepinephrine Re-uptake Inhibitor (SNRI) and tricyclic antidepressants (TCAs). The symptoms of serotonin syndrome may include mental-status changes, autonomic instability, neuromuscular abnormalities, and/or gastrointestinal symptoms.

Drugs affecting gastrointestinal activity
Methadone may have an effect on other substances as a consequence of reduced gastrointestinal motility.

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.

Grapefruit juice
Cytochrome P450 (CYP) 3A4 is the main CYP isozyme involved in methadone metabolism. Grapefruit juice contains inhibitors of intestinal CYP3A, on the steady-state pharmacokinetics of methadone. Grapefruit juice administration is associated with a modest increase in methadone bioavailability, which is not expected to endanger patients. However, it cannot be excluded that a much stronger effect may occur in some patients, and thus grapefruit juice intake is not recommended during methadone maintenance treatment, in particular in patients initiating such a treatment.

Gabapentinoids
The concomitant use of opioids and gabapentinoids (gabapentin and pregabalin) increases the risk of opioid overdose, respiratory depression, and death.

Cannabidiol

Concomitant administration of cannabidiol may result in increased plasma concentrations of methadone.

The subject formulation contains colouring additives that are permitted colour additives for foods within the EC. These colours are synthetic azo dyes and are recognised to produce sensitisation manifest as bronchospasm, rhinitis and skin rashes. Persons already sensitised to aspirin may react adversely when exposed to these dyes.

4.6 Fertility, pregnancy and lactation

Fertility
Long-term use of opioids may decrease sex hormone levels which could cause fertility problems in humans (see section 4.4).

Studies in men on methadone maintenance programmes have shown that methadone reduces serum testosterone and markedly depresses the ejaculate volume and sperm motility. The sperm counts of methadone subjects were twice that of controls but this reflected the lack of dilution from seminal secretions.

Pregnancy
There is insufficient evidence on which to determine the safety profile of methadone in pregnancy, therefore it should only be used where the benefits of a monitored methadone detoxification program outweigh the potential risks (see section 5.3).

Like other opiates, methadone crosses the placenta during pregnancy, and most neonates born to mothers on methadone maintenance will suffer from respiratory depression and neonatal abstinence syndrome if left untreated.

Abstinence syndrome may not occur in the neonate for some days after birth. Therefore in addition to initial monitoring for respiratory depression neonates should undergo prolonged monitoring for signs and symptoms of withdrawal.

Methadone is not recommended for use during labour because its prolonged duration of action increases the risk of respiratory depression in the neonate (see section 4.4).

Lactation
Methadone is excreted in breast milk at low levels. It is distributed into breast milk, with a mean ratio of milk to plasma concentration of 0.44. However, doses of methadone to the infant via breast milk are estimated at 3% of maternal doses.

The decision to recommend breast-feeding should take into account clinical specialist advice and consideration should be given to whether the woman is on a stable maintenance dose of methadone and any continued use of illicit substances. If breastfeeding is considered, the dose of methadone should be as low as possible. Prescribers should advise breastfeeding women to monitor the infant for sedation and breathing difficulties and to seek immediate medical care if this occurs. Although the amount of methadone excreted in breast milk is not sufficient to fully suppress withdrawal symptoms in breast-fed infants, it may attenuate the severity of neonatal abstinence syndrome. If it is necessary to discontinue breastfeeding it should be done gradually, as abrupt weaning could increase withdrawal symptoms in the infant.

4.7 Effects on ability to drive and use machines

Methadone has moderate influence on the ability to drive and use machines. In common with other opioids, Pinadone may produce orthostatic hypotension and drowsiness in ambulatory patients. They should be cautioned, therefore, against driving vehicles, operating machinery or other activities requiring vigilance.

4.8 Undesirable effects

Adverse reactions are ranked under headings of frequency using 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)

Adverse reactions denoted by a hash (#) appear to be more common in ambulatory patients and in those receiving oral therapy.

Endocrine disorders
Not known: adrenal insufficiency (see section 4.4)

Metabolism and nutrition disorders
Not known: Hypoglycaemia.

Psychiatric disorders
Common: confusion#.
Not known: Euphoria has been reported at higher doses in tolerant subjects, dependence.

Nervous system disorders
Very common: dizziness#, drowsiness#, light-headedness#.
Not known: syncope, serotonin syndrome (see section 4.4)

Eye disorders
Not known: miosis

Cardiac Disorders
Rare: ECG changes including QT prolongation and Torsade de Pointes, usually in patients with risk factors or receiving high doses of methadone (see section 4.4).

Vascular disorders
Rare: hypotension and collapse.

Respiratory, thoracic and mediastinal disorders
Not known: Respiratory depression (see section 4.4), central sleep apnoea syndrome.

Gastrointestinal disorders
Very common: nausea#, vomiting#, dry mouth#, constipation.

Hepatobiliary disorders
Not known: Methadone, in common with other opioids may cause spasm of the biliary tract (see section 4.3).

Skin and subcutaneous tissue disorders
Very common: sweating#.

Renal and urinary disorders
Common: Urinary retention or hesitancy.
Not known: Methadone, in common with other opioids may cause spasm of the renal tracts (see section 4.3).

Reproductive system and breast disorders
*Not known:*Prolonged use of methadone in men has been reported to be associated with the development of gynaecomastia and impaired fertility (see section 4.6), sexual dysfunction (erectile, libido, orgasm dysfunction), decreased sex hormones (see section 4.4 and section 4.6).

Withdrawal (abstinence) syndrome: Chronic use of opioid analgesics may be associated with the development of physical dependence. An abstinence syndrome may be precipitated when opioid administration is suddenly discontinued or opioid antagonists administered. Withdrawal symptoms that may be observed after discontinuation of opioid use include:
Body aches, diarrhoea, piloerection, anorexia, nervousness or restlessness, rhinorrhoea, sneezing, tremors or shivering, abdominal colic, nausea, sleep disturbance, unusual increase in sweating and yawning, weakness, tachycardia and unexplained fever. With appropriate dose adjustments and gradual withdrawal these symptoms are usually mild.

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, Website: www.hpra.ie.

4.9 Overdose

Symptoms and Signs
The symptoms and signs of overdosage with methadone parallel those for other opioids, namely profound respiratory depression, pin-point pupils, hypotension, circulatory failure and pulmonary oedema, coma and death.

Hypoglycaemia has been reported.

Mydriasis may replace miosis as asphyxia intervenes. Drowsiness, floppiness, pin-point pupils and apnoea have been reported in children.
Toxic leukoencephalopathy has been observed with methadone overdose.

Treatment
General supportive measures, including ECG monitoring, should be employed as required.

The specific opioid antagonist naloxone is the treatment of choice for the reversal of coma and the restoration of spontaneous respiration, the literature should be consulted for details of appropriate dosage. It should be noted that QT prolongation will not be reversed by naloxone.

In opioid dependent patients the administration of the recommended dose of an opioid antagonist may precipitate an acute withdrawal syndrome. The severity of this syndrome will depend on the degree of physical dependence and the dose of the antagonist administered. The use of an opioid antagonist in such a person should be avoided if possible. If it must be used to treat serious respiratory depression in the physically dependent patient the antagonist should be administered with extreme care and by titration with smaller than usual doses of the antagonist.

Patients should be monitored closely for at least 48 hours after apparent recovery in case of relapse, since the duration of action of the antagonist may be substantially shorter than that of methadone.

The use of other respiratory or central stimulants is not recommended.

Acidification of the urine will enhance urinary excretion of methadone.

Methadone is not dialysable by either peritoneal or haemodialysis.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Analgesics- Diphenylpropylamine derivatives; ATC Code: N07BC02.

Mechanism of action
Methadone is a synthetic opioid analgesic, structurally different from morphine, with a broad spectrum of receptor affinities. Its predominant opiate activity is as a mu agonist, though it is also active at the delta and kappa opiate receptors. In addition, two non-opiate activities (N-methyl-d-aspartate (NMDA) antagonism and monoamine uptake inhibition) also contribute to its analgesic effects.

Methadone is a racemate, the opioid agonist activities residing predominantly with the R(-)-enantiomer and the monoamine uptake inhibition with the S(+)-enantiomer; the two enantiomers exhibit similar potencies as NMDA-receptor antagonists. Methadone's inhibition of monoamine re-uptake activity does not correlate with its mu receptor affinities.

Pharmacodynamic effects
The combination of opioid agonism and NMDA antagonism by methadone produces an additive analgesic response while limiting opioid tolerance. Additionally, the prevention of reuptake of the monoamines serotonin and norepinephrine in the

periaquaductal gray (PAG) improves pain control, particularly in the case of neuropathic pain, by blocking the downward modulation of pain via the descending tracts of the PAG. The delta receptor agonist activity of methadone leads to desensitization of this receptor and may also account for the reduction of opioid tolerance associated with methadone.

5.2 Pharmacokinetic properties

Absorption
Methadone is well absorbed by the gastrointestinal tract with an oral bioavailability of approximately 75% (range 36 to 100). Peak plasma concentrations occur at 2.5 to 4 hours post-dose. Intestinal first-pass metabolism accounts for the less than complete bioavailability, which is consistent with a predicted first pass extraction of 20% by CYP3A4.

Distribution
Methadone is bound to plasma proteins predominantly to the alpha 1-acid glycoprotein, with an unbound fraction of 11% in healthy volunteers.

Methadone is highly distributed into tissues, with volume of distribution of approximately 4 l/kg (range 2 to 13 l/kg). The stereoselectivity of methadone distribution is unclear. Methadone has a rapid and extensive initial distribution phase. Methadone is also secreted in saliva; with chronic use, salivary concentrations may be 10-fold those measured simultaneously in the blood.

Metabolism
Methadone undergoes N-demethylation to 2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrilidine (EDDP) with CYP3A4 being the main enzyme responsible. However, other CYP450 enzymes are also likely to be involved; CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C18, CYP2C19 and CYP2D6 have all been mentioned as also playing a role, though there is little consensus on the rank order of these activities.

Stereoselective metabolism of S(+)- and R(-)-methadone has been reported. Using human drug-metabolizing CYPs from baculovirus-infected cell supersomes, it was observed that CYP2B6 preferentially metabolised S(+)-methadone, CYP2C19 preferentially metabolised R(-)-methadone and CYP3A4 metabolised both enantiomers at equivalent rates. However, recombinant CYP3A4 had approximately 4-fold higher activity for R(-)-methadone than for S(+)- methadone; CYP 2C8 had lower activity with respect to R(-)-methadone but equivalent activity to CYP3A4 with respect to S(+)-methadone. However, there is also one report of no stereospecificity in the metabolism of methadone by human liver microsomes.

The clearance of methadone is increased by chronic dosing due to auto-induction of CYP3A4.

Elimination
Elimination of methadone occurs principally by metabolism, followed by urinary and faecal excretion of the metabolites, though there is some renal excretion of unchanged methadone.

Total methadone clearance is 0.095 l/min, but is subject to wide interindividual variation, up to 100-fold. Although no difference in total clearance has been observed between enantiomers, unbound clearance is lower for R(-)- than for S (+)-methadone (4.6 l/min versus 7.8 l/min, respectively). After parenteral administration, plasma concentrations of methadone decrease in a biexponential manner, with a mean terminal phase half-life of approximately 22 hours, (range 5-130 h). Longer values of 40 hours have been determined for the active R(-)-enantiomer.

Urinary and faecal excretion of methadone and N-demethylated metabolites increase from 22% in acute dosing, to 62% in chronic dosing.

Although methadone is mostly eliminated by metabolism, a significant proportion of the dose is excreted via the kidney. Up to 19% of the dose, was found to be eliminated by this route. Renal excretion of methadone is pH dependent; data suggests that it may only be a significant route of elimination at urinary pH <6.

Special Patient Populations

Elderly people
Methadone clearance does not appear to be markedly affected by age, though a slight decrease has been observed over age 65.

Renal impairment
Although methadone is mostly eliminated by metabolism, a significant proportion of the dose is excreted via the kidney.

5.3 Preclinical safety data

Carcinogenesis and Mutagenicity

Long term carcinogenicity tests in rodents did not reveal any evidence of methadone-related neoplasia.

Methadone did not exhibit demonstrable mutagenic activity in a wide range of standard *in vitro* and *in vivo* mutagenicity assays.

However, in a dominant lethal assay in mice, treatment with methadone at doses between 1 and 6mg/kg was associated with increased pre-implantation deaths and chromosomal aberrations of sperm cells when compared with controls.

Reproductive toxicology

No teratogenic effects have been observed in standard teratogenicity studies in rats and rabbits given methadone at doses from ten to fifty times the average daily human maintenance dose. Developmental abnormalities of the central nervous system have been reported in non-standard studies in hamsters and mice given high doses in early pregnancy.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Propylene glycol
Benzoic acid
Sodium hydroxide
Maltitol Liquid (E965)
Hydroxyethylcellulose
Purified water
Sunset yellow (E110)
Green S (E142).

6.2 Incompatibilities

Syrup preserved with hydroxybenzoate esters may be unsuitable for extemporaneous dispensing as physical incompatibility with methadone hydrochloride has been reported.

6.3 Shelf life

20ml, 25ml, 30ml, 35ml, 40ml, 45ml, 50ml, 55ml, 60ml HDPE bottles:	6 months
100ml, 500ml, 5L HDPE bottle:	2 years
100ml Amber glass bottle:	3 years
500ml and 1L Amber glass bottle:	2 years
In-use shelf life for Amber Glass Bottles only:	3 months

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

Type III amber glass bottle with tamper evident polypropylene cap and a LDPE liner containing 100ml, 500 ml or 1L.

Jaycare Pharma HDPE bottle with tamper evident polypropylene cap and a LDPE liner containing 500 ml.

BXL Cascelloid HDPE bottle with tamper evident polypropylene cap and a LDPE liner containing 20 ml, 25ml, 30ml, 35ml, 40ml, 45ml, 50ml, 55 ml, 60ml and 100ml.

5L HDPE container with tamper evident HDPE cap.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

Methadone hydrochloride is a controlled drug under the Misuse of Drugs Act SI 12 of 1977.

7 MARKETING AUTHORISATION HOLDER

Pinewood Laboratories Ltd
Ballymacarbry
Clonmel
Co. Tipperary
Ireland

8 MARKETING AUTHORISATION NUMBER

PA0281/061/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 15th November 1995

Date of last renewal: 15th November 2005

10 DATE OF REVISION OF THE TEXT

May 2023