Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Methadone Hydrochloride Sugar Free 1mg/1ml Oral Solution

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1ml of solution contains 1mg methadone hydrochloride

Excipients with known effect:
Liquid Maltitol (E965) – 0.55g/ml
Methyl parahydroxybenzoate (E218) – 1.2mg/ml
Propyl parahydroxybenzoate (E216) – 0.3mg/ml
Propylene Glycol (E1520) – 20.7mg/ml

For a full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Oral Solution.

A green solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

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
The subject formulation contains 2.5 times the concentration of methadone found in methadone linctus and is suitable ONLY for use as substitution or maintenance therapy of narcotic dependence. The decision to maintain a patient on a long-term opioid prescription should be an active decision agreed between the clinician and patient with review at regular intervals (usually at least three-monthly, depending on clinical progress).

Adults: Initial dosage is usually 10 – 20mg per day, increasing by 10 – 20mg per day until there are no signs of withdrawal or intoxication. The usual dose is 40 – 60mg per day.

The dose is individually adjusted according to the degree of dependence with the aim of gradual reduction, and bearing in mind the clinical status, including hepatic and renal function of the patient.

Dosage in Pregnancy: Drug withdrawal needs to be achieved 4 – 6 weeks before delivery if neonatal abstinence syndrome is to be certain to be avoided, but abrupt withdrawal can cause intrauterine death. Detoxification to abstinence is least stressful to mother and foetus if undertaken during the mid trimester.

Abstinence syndrome may not occur in the neonate for some days after birth. In the event that withdrawal is not possible prior to delivery, methadone administered to the mother may result in prolonged respiratory depression in the neonate and the administration of opioid antagonists may be required.

Elderly: In the case of elderly or ill patients repeated doses should only be given with extreme caution.

Children: Not recommended for children.

Renal Impairment: Methadone 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 50ml/minute and to a minimum of 12-hourly when the GFR is below 10ml/minute.

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

Method of Administration
For oral administration

4.3 Contraindications

Respiratory depression, obstructive airways disease, acute asthma attack, concurrent administration with MAO inhibitors, including moclobemide or within 2 weeks of discontinuation of treatment with them (see section 4.5). Concurrent use of other central nervous system depressants. Use during labour is not recommended, the prolonged duration of action increases the risk of neonatal depression. Methadone is not suitable for children (serious risk of toxicity).

Known hypersensitivity to methadone or any of the excipients (see section 6.1).

Patients dependent on non-opioid drugs.
Patients with acute alcoholism (see section 4.5), head injury and raised intra-cranial pressure (further rise in intracranial pressure - see section 4.8, papillary response affected).
As with other opioids, Methadone Oral Solution is contraindicated in patients with ulcerative colitis, since it may precipitate toxic dilation or spasm of the colon.
It should not be administered to patients with severe hepatic impairment as it may precipitate hepatic encephalopathy.

Patients with biliary and renal tract spasm.

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 pruritis 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.

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.

Abuse or intentional misuse of methadone 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.

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.

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.

Hepatic disorders

Caution as methadone may precipitate porto-systemic encephalopathy in patients with severe liver damage. As with other opioids, methadone may cause constipation, which is particularly dangerous in patients with severe hepatic impairment. Measures to avoid constipation should be initiated early.

Adrenal insufficiency

Opioid analgesics may cause reversible adrenal insufficiency requiring monitoring and glucocorticoid replacement therapy. Symptoms of adrenal insufficiency may include nausea, vomiting, loss of appetite, fatigue, weakness, dizziness, or low blood pressure.

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

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)

Neonates/children

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.

As there is a risk of greater respiratory depression in neonates and because there are currently insufficient published data on the use in children, methadone is not recommended in those under 16 (See sections 4.2, 5.2).

There are reports of neonates exposed to methadone during pregnancy developing visual disorders, including reduced visual acuity, strabismus and nystagmus. The causal relationship to methadone in isolation has not been established as factors such as other drugs taken during pregnancy e.g. benzodiazepines, intake of alcohol, and drugs used to treat neonatal abstinence syndrome e.g. phenobarbital, could play a role in the adverse reactions seen.

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, as with other opiates, has the potential to increase intracranial pressure especially where it is already raised.

There is an increased risk of endocrinopathy including hypoadrenalism and hypogonadism, especially with long-term use.

Methadone Oral Solution should be used with caution in the presence of hypothyroidism, adrenocortical insufficiency, hypopituitarism, prostatic hypertrophy, hypotension, inflammatory or obstructive bowel disorders or myasthenia gravis and shock. Extreme caution should be exercised when administering to patients with phaeochromocytoma, since aggravated hypertension may be a risk.

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 development of prolonged QT interval, e.g. in case 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.

<u>Risk from concomitant use of sedative medicines such as benzodiazepines or related drugs:</u>

Concomitant use of Methadone 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 Methadone 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).

Excipient Warnings

- This medicine contains methyl (E218) and propyl parahydroxybenzoates (E216). These may cause allergic reactions (possibly delayed).
- Liquid maltitol (E965) 0.55g/ml. Patients with rare hereditary problems of fructose intolerance should not take this medicine.
- Propylene glycol. This medicine contains 20.7mg of propylene glycol (E1520) in each ml.

4.5 Interaction with other medicinal products and other forms of interaction

Methadone is metabolised in the liver to inactive metabolites via the mixed-function oxidase system. Interactions occur with enzyme inducers and inhibitors.

Cimetidine: Potentiation of opiate action due to displacement of methadone from protein binding sites.

Rifampicin: Reduced opiate effect due to increased metabolism.

Anticonvulsants: Drugs such as phenytoin, phenobarbital, carbamazepine and primidone may enhance methadone metabolism with the risk of inducing a withdrawal syndrome.

Neuromuscular Blocking Agents: may enhance the general depressant effects of methadone.

Antiretroviral Agents such as nevirapine, efavirenz, nelfinavir and some protease inhibitors: These agents may decrease plasma concentrations of methadone by increasing its hepatic metabolism. Methadone may increase the plasma concentration of some drugs e.g. nelfinavir and zidovudine, whereas concentrations of others may be decreased, e.g. abacavir and amprenavir. Narcotic withdrawal syndrome has been reported in patients treated with some antiretroviral agents and methadone concomitantly. Methadone maintained patients beginning antiretroviral therapy should be monitored for evidence of withdrawal and methadone dose should be adjusted accordingly.
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 Warnings and Precautions). 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.

Urinary clearance of methadone is increased by acidic urine and decreased in alkaline urine. Drugs and preparations altering urinary pH may thus affect methadone pharmacokinetics. It should be noted that vegetarians tend to produce alkaline urine, and dietary habits may thus be relevant to methadone dosage.

The subject formulation contains colouring additives that are permitted colour additives for foods within the EC.

CNS drugs
CNS Depressants: Major and minor tranquillisers (including phenothiazines), barbiturates, sedatives and tricyclic anti-depressants may result in increased CNS depression, respiratory depression and hypotension. There are reports that antidepressant drugs (e.g. fluvoxamine and fluoxetine) may increase serum levels of methadone, whereas the plasma concentration of desipramine may be increased by methadone.

Psychotropic Drugs: May potentiate the analgesic effects of methadone.

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

Sedative medicines such as benzodiazepines or related drugs:
The concomitant use of opioids with sedative medicines such as benzodiazepines or related drugs increased 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).

Centrally acting alpha-adrenergic blockers
There is an increased risk of hypotension, cognitive effects and ECG changes (including PR interval and QT interval prolongation) when methadone is co-administered with centrally acting alpha-adrenergic blockers (lofexidine and clonidine).

Opioid Agonist
Analgesics: Additive CNS depression, respiratory depression and hypotension.

Naloxone: Antagonises the analgesic, CNS and respiratory depressant effects of methadone.

Naltrexone: Administration of naltrexone to a patient addicted to methadone will rapidly precipitate long term withdrawal symptoms.

Buprenorphine/Pentazocine: Administration to a patient addicted to methadone may precipitate withdrawal symptoms.

Alcohol: May induce serious respiratory depression and hypotension.

MAOI's: Concomitant use may result in CNS excitation or depression and may prolong and enhance the respiratory depressant effects of methadone. Opioids and MAOIs used together may cause fatal hypotension and coma.

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). Methadone may also increase the plasma concentration of fluconazole.

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

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.

Other Drugs:
Methadone is a weak serotonin uptake inhibitor. There is an increased risk of serotonin syndrome when methadone is co-administered with other serotonergic drugs (e.g. SSRIs, SNRIs, TCAs, MAOIs, serotonergic anti-emetics, serotonergic anti-migraine drugs). This is not an exhaustive list.
Methadone may have an effect on other drugs as a consequence of reduced gastro-intestinal motility.

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

Pregnancy Tests:
Methadone may interfere with the urine testing for pregnancy.

St. John's Wort:
May lower plasma concentrations of methadone.

Co-administration of Methadone with metamizole, which is an inducer of metabolising enzymes including CYP2B6 and CYP3A4 may cause a reduction in plasma concentrations of Methadone with potential decrease in clinical efficacy. Therefore, caution is advised when metamizole and Methadone are administered concurrently; clinical response and/or drug levels should be monitored as appropriate.

4.6 Fertility, pregnancy and lactation

Fertility
Methadone does not appear to impair human female fertility.

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. (See 4.8 undesirable effects)

Pregnancy
Methadone administered to pregnant women for the management of opioid addiction has the potential for several adverse effects on the foetus and neonate. A careful benefit/risk assessment must be made. Apart from the risk of prolonged respiratory depression in the neonate, the immediate problems are withdrawal syndrome in utero and following birth and low birthweight; increased stillbirth rates have also been reported.

The effects of methadone itself on pregnancy and infants born to methadone-treated mothers are difficult to assess in view of the complicating factors such as poor prenatal care, poor maternal nutrition, smoking, poor environmental and social conditions. Most studies have associated methadone with a low birthweight but methadone has not convincingly 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.

It should not be used during labour (see section 4.3).

Breast Feeding
Methadone is excreted in breastmilk at low levels. 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

Driving may be severely affected during and after treatment with Methadone. The time after which such activities may be safely resumed is extremely patient dependent and must be decided by the Physician.

4.8 Undesirable effects

Cardiac Disorders
Bradycardia and palpitation can occur. Cases of QT prolongation and torsades de pointes have been rarely reported. (See section 4.4, 4.5).

Ear and labyrinth disorders
Vertigo.

Endocrine Disorders
Raised prolactin levels with long-term administration.

Rare: Evidence of hypoadrenalism has been found in chronic methadone addicts. Findings consistent with both deficient ACTH production and subsequent secondary hypoadrenalism and methadone induced primary adrenal cortical hypofunction have been reported.
Not known: Hypogonadism (especially with long-term use).

Eye Disorders
Miosis, dry eyes, nystagmus. In children and neonates exposed to methadone during pregnancy: blurred vision, strabismus, visual acuity reduced (see section 4.4).

Gastrointestinal disorders
Nausea and vomiting particularly at the start of treatment can occur. Constipation, dry mouth.

General disorders
Hypothermia.
Partial tolerance has been found to develop to the nauseant, anorectic, miotic, sedative, respiratory depressant and cardiovascular effects of methadone on repeated daily administration. Tolerance to the constipating effect does not develop as fully.

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.

Hepatobiliary Disorders
Methadone may cause spasm of the biliary tract in common with other opioids.

Nervous System Disorders
Drowsiness dizziness and headache. Methadone has the potential to increase intracranial pressure, particularly in circumstances where it is already raised.

Rare: 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.

Psychiatric disorders
Dependence, confusion particularly at the start of the treatment can occur.
Changes of mood and hallucinations are occasionally reported. Restlessness and decreased libido.
Rare: Euphoria has been reported at high doses in tolerant subjects.

Renal and urinary disorders
Less commonly micturition difficulties are observed. Methadone may cause spasm of the renal tract, in common with other opioids. It also possesses antidiuretic properties.

Reproductive system and breast disorders
Galactorrhoea, dysmenorrhoea, amenorrhoea.
Rare: 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 66.9mg) were reduced by over 50% compared to 16 heroin addicts and 43 narcotic-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.

Prolonged use of methadone in men has been reported to be associated with the development of gynaecomastia and impaired fertility.

Respiratory, thoracic and mediastinal disorders
Exacerbation of existing asthma as a result of histamine release, dry nose, respiratory depression, central sleep apnoea syndrome.

Skin and subcutaneous tissue disorders
Rashes. Long-term administration may produce excessive sweating. Pruritus and urticaria as a result of histamine release.

Vascular disorders
Orthostatic hypotension, facial flushing. Methadone can produce hypotension as a result of histamine release.

A number of heroin addicts 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 addicts, 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.
Metabolism and nutrition disorders
Hypoglycaemia (frequency not known)

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 PharmacovigilancWebsite: www.hpra.ie.

4.9 Overdose

Symptoms: Serious overdosage 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 overdosage, particularly by the intravenous route, apnoea, circulatory collapse, cardiac arrest and death may occur. Hypoglycaemia has been reported. Toxic leukoencephalopathy has been observed with methadone overdose.

Treatment: A patient 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. Nalorphine (0.1mg per Kg) or levallorphan (0.02mg per Kg) should be given intravenously as soon as possible and repeated, if necessary, every 15 minutes. 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 it should be administered with great care.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC code: N07 BC02

Pharmacotherapeutic group: (Nervous system, other nervous system drugs, drugs used in addictive disorders, methadone).

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 on 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 pA2 value similar to its anti-antagonism of morphine. Like many basic drugs 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 gastro-intestinal tract, but undergoes fairly extensive first pass metabolism. It is bound to albumin and other plasma proteins and to tissue proteins (probably lipoproteins), the concentrations in lung, liver and kidneys being much higher than in blood. The pharmacokinetics of methadone are unusual, in that there is extensive binding to tissue proteins and fairly slow transfer between some parts of this tissue reservoir and the plasma.

Distribution
With an intramuscular dose of 10mg, a peak plasma concentration of 75μg/L^{-1} is reached in one hour. With regular oral doses of 100 – 120mg daily, plasma concentrations rise from trough levels of approximately 500μg/L to a peak of about 900μg/L in 4 hours. Marked variations in plasma level occur in dependent persons on a stable dose of oral methadone, without any relation to symptoms. Methadone is secreted in sweat and found in saliva and in high concentrations in gastric juice. The concentration in cord blood is about half the maternal level.

Biotransformation
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 (mean 25) hours reflecting only clearance.

Elimination
In the first 96 hours after administration, 15 – 60% can be recovered from the urine, and as the dose is increased so a higher proportion of unchanged methadone is found there.

Acidification of the urine can increase the renal clearance by a factor of at least three, and thus appreciably reduce the half time of elimination.

Patients with severe hepatic dysfunction have a marked increase in half-life (35.5 hours).

5.3 Preclinical safety data

Methadone hydrochloride is a well known and long established substance. There have been no pharmacological or toxicological issues raised with this product. Care should be taken however with the use of this product in pregnancy. (See Section 4.6 on use during pregnancy and lactation).

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Propylene Glycol (E1520)
Methyl parahydroxybenzoate (E218)
Propyl parahydroxybenzoate (E216)
Liquid Maltitol (E965)
Purified Water
Caramel (E150)
Patent Blue V (E131)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Amber (Type III) glass bottles: Store below 25°C. Store in the original package (to protect from light).

6.5 Nature and contents of container

Amber (Type III) glass bottles with capacity of 500ml.
Closures are:
HDPE, child resistant, EPE wadded, tamper evident.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.
Any unused product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Taw Pharma (Ireland) Ltd
104 Lower Baggot Street
Dublin 2
Dublin
D02 Y940
Ireland

8 MARKETING AUTHORISATION NUMBER

PA23081/011/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 27 July 1998

Date of last renewal: 27 July 2008

10 DATE OF REVISION OF THE TEXT

July 2023