SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Methadone Hydrochloride DTF 1mg/1ml Oral Solution

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Methadone Hydrochloride BP 5mg/5ml

Excipients with known effect:

Liquid Maltitol
Sucrose
Methyl hydroxybenzoate (E218)
Propyl hydroxybenzoate (E216)
Propylene Glycol
Tartrazine (E102)
Sunset yellow (E110)

For full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Oral Solution

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

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

For use as an analgesic for moderate to severe pain.

4.2. Posology and method of administration

Treatment goals and discontinuation

Before initiating treatment with methadone, 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).

Posology

Addiction:

Adults: Initially 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 adjusted according to the degree of dependence, with the aim of gradual reduction.

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

Children: Not recommended for children.

Pain:

Adults: Usual single dose 5 to 10mg orally. 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 to 10mg, 6 to 8 hourly, later adjusted to the degree of pain relief obtained.

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

Children: Not suitable.

Method of Administration
For oral administration only

4.3. Contraindications

- Respiratory depression, obstructive airways disease. Use during an acute asthma attack is not recommended.
- Acute alcoholism (see section 4.5).
- Concurrent administration with MAO inhibitors, including moclobemide, or within 2 weeks of discontinuation of treatment with them (see section 4.5).
- Patients dependent on non-opioid drugs.
- 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).

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Raised intracranial pressure (further rise in intracranial pressure – see section 4.8: papillary response affected) or head injury.
- Phaeochromocytoma.
- Risk of paralytic ileus (including drug induced gastrointestinal hypotonia).

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.

Caution should be exercised in patients with hepatic dysfunction or renal dysfunction.

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

Opioid use disorder (abuse and dependence)

Methadone is an opioid a narcotic 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.
Tolerance and dependence may occur as with morphine.

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 methadone 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 methadone 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 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.

A comprehensive patient history should be taken to document concomitant medications, including over-the-counter medicines and medicines obtained on-line, and past and present medical and psychiatric conditions. Patients may find that treatment is less effective with chronic use and they may express a need to increase the dose to obtain the same level of pain control as initially experienced. Patients may also supplement their treatment with additional pain relievers. These could be signs that the patient is developing tolerance. The risks of developing tolerance should be explained to the patient.

Methadone is controlled under the Misuse of Drugs Act 1971 (Schedule 2).

Drug withdrawal syndrome

Prior to starting treatment with any opioids, a discussion should be held with patients to put in place a withdrawal strategy for ending treatment with methadone.

When used for substitution or maintenance therapy 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).

Drug withdrawal syndrome may occur upon abrupt cessation of therapy or dose reduction. When a patient no longer requires therapy, it is advisable to taper the dose gradually to minimise symptoms of withdrawal.

The opioid drug withdrawal syndrome is characterised by some or all of the following: restlessness, lacrimation, rhinorrhoea, yawning, perspiration, chills, myalgia, mydriasis and palpitations.

Other symptoms may also develop including irritability, agitation, anxiety, hyperkinesia, tremor, weakness, insomnia, anorexia, abdominal cramps, nausea, vomiting, diarrhoea, increased blood pressure, increased respiratory rate or heart rate.

If women take this drug during pregnancy, there is a risk that their new-born infants will experience neonatal withdrawal syndrome.

Hyperalgesia
Patients on long-term opioid therapy for analgesia may present with increased pain diagnosed as hyperalgesia. This might be qualitatively and anatomically distinct from pain related to disease progression or to breakthrough pain resulting from development of opioid tolerance. Pain associated with hyperalgesia tends to be more diffuse than the pre-existing pain and less defined in quality. Symptoms of hyperalgesia may resolve with a reduction of opioid dose.

Respiratory depression

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).

Hepatic disorders
Caution as methadone may precipitate porto-systemic encephalopathy in patients with severe liver damage.

As with other opioids, methadone may cause troublesome constipation, which is particularly dangerous in patients with severe hepatic impairment, and measures to avoid constipation should be initiated early.

Biliary tract disorders.

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)

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.

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

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

Methadone should be used with caution in patients with history of asthma (see section 4.3), convulsive disorders, depressed respiratory reserve, hypothyroidism, prostatic hyperplasia, hypotension, shock, inflammatory or obstructive bowel disorders or myasthenia gravis. 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 development of prolonged QT interval, e.g. in case of:
- history of cardiac conduction abnormalities,
- advanced heart disease or ischaemic heart disease,
- liver disease,
- family history of sudden death,
- electrolyte abnormalities, i.e. hypokalaemia, hypomagnesaemia
- concomitant treatment with 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.

Caution should be exercised in patients who are concurrently taking CNS depressants.

Risk from concomitant use of sedative medicines such as benzodiazepines or related drugs:

Concomitant use of Methadone 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 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).

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.

Excipient warnings:
This product contains:

- E102 and E110, which may cause allergic reactions.
- Liquid maltitol. Patients with rare hereditary problems of fructose intolerance should not take this medicine.
- Sucrose. Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine. The product contains 0.9g of sucrose per 5ml and should be taken into account in patients with diabetes mellitus. It may be harmful to teeth.
- Methyl and Propyl hydroxybenzoates. These may cause allergic reactions (possibly delayed)
- Propylene glycol. This medicine contains 155.6mg propylene glycol per 5ml. While propylene glycol has not been shown to cause reproductive or developmental toxicity in animals or humans, it may reach the foetus and was found in milk. As a consequence, administration of propylene glycol to pregnant or lactating patients should be considered on a case by case basis. Medical monitoring is required in patients with impaired renal or hepatic functions because various adverse events attributed to propylene glycol have been reported such as renal dysfunction (acute tubular necrosis), acute renal failure and liver dysfunction.

4.5. Interaction with other medicinal products and other forms of interaction

MAOI's:
The concurrent use of MAOI's is contraindicated (see 4.3 Contraindications) as they may prolong and enhance the respiratory depressant effects of methadone.
CNS depressants:
Anaesthetics, hypnotics (including benzodiazepines, chloral hydrate and chlormethiazole), anxiolytics, sedatives, barbiturates, phenothiazines, some other major tranquillizers and tricyclic antidepressants may increase the general depressant effects of methadone when used concomitantly. (See 4.4

Special warnings and precautions for use). Antipsychotics may enhance the sedative effects and hypotensive effects of methadone.
The concomitant use of opioids and gabapentinoids (gabapentin and pregabalin) increases the risk of opioid overdose, respiratory depression, and death.

Methadone may increase desimipramine levels by up to a factor of two.

There are reports that antidepressant drugs (e.g. fluvoxamine and fluoxetine) may increase serum levels of methadone.

Alcohol may enhance the sedative and hypotensive effects of methadone and increase respiratory depression.

Cannabidiol

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

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.

Histamine H_2 Antagonists:
Histamine H_2 antagonists such as cimetidine, can reduce the protein binding of methadone resulting in increased opiate action.

Antibacterials
Rifampicin*:* Reduced plasma levels and increased urinary excretion of methadone can occur with concurrent administration of rifampicin. Adjustment of the dose of methadone may be necessary.

Ciprofloxacin: Plasma levels of methadone may increase with concurrent administration of ciprofloxacin due to inhibition of CYP 1A2 and CYP 3A4. Reduced serum concentrations of ciprofloxacin may occur. Concomitant use may lead to sedation, confusion and respiratory depression.

Erythromycin: Theoretically this may increase methadone levels due to decreased methadone metabolism.

Antifungals: *Fluconazole, voricanozole and ketoconazole:* May raise methadone levels, due to decreased methadone metabolism.

Anticonvulsants (Phenytoin, Phenobarbital, Carbamazepine and Primidone):

Induces the metabolism of methadone and there may be a risk of precipitating withdrawal syndrome. Adjustment of the dose of methadone should be considered.

pH of urine:
Drugs that acidify or alkalinise the urine may have an effect on clearance of methadone as it is increased at acidic pH and decreased at alkaline pH.

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

Opioid antagonists:
Naloxone and naltrexone antagonises the analgesic, CNS and respiratory depressant effects of methadone and can rapidly precipitate withdrawal symptoms (See Section 4.9 Overdose). Similarly buprenorphine and pentazocine may precipitate withdrawal symptoms.

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

Cyclizine and other sedating antihistamines
May have additive psychoactive effects; antimuscarinic effects at high doses.

Other Drugs:
Methadone may have an effect on other drugs as a consequence of reduced gastro-intestinal motility.
Pregnancy Tests:
Methadone may interfere with the urine testing for pregnancy.

Cytochrome P450 3A4 inhibitors:
Methadone clearance is decreased when co-administered with drugs which inhibit CYP3A4 activity, such as some anti-HIV agents, macrolide antibiotics, cimetidine and azole antifungal agents (since the metabolism of methadone is mediated by the CYP3A4 isoenzyme).

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

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

Drugs affecting gastric emptying:

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

Antiarrhythmics:
Methadone delays the absorption of mexiletine.

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

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).

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).

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

There is no evidence of safety in human pregnancy. A careful risk/benefit assessment should be made before administration to pregnant women because of possible adverse effects on the foetus and neonate including respiratory depression, low birth weight, neonatal withdrawal syndrome and increased rate of stillbirths. However, methadone has not been associated with congenital malformations.
It may be necessary to increase the dose of methadone if withdrawal symptoms develop. Increased clearance and reduced plasma levels have been reported during pregnancy.

Regular use during pregnancy may cause drug dependence in the foetus, leading to withdrawal symptoms in the neonate.

If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available.

During labour there is a risk of gastric stasis and inhalation pneumonia in the mother and foetal distress. Methadone should not be used in labour (see 4.3 Contraindications).

Administration during labour may depress respiration in the neonate and an antidote for the child should be readily available.

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.

Specialist care for obstetric and paediatric staff with experience in such management is required. If breast feeding is considered, the dose of methadone should be as low as possible and the infant monitored to avoid sedation. Breastfed infants may develop physical dependence and exhibit withdrawal symptoms.

Reports of visual disorders have been reported in neonates following exposure to methadone during pregnancy. However, other factors have also been present and a definitive causal link to methadone has not been established (see section 4.4).

4.7. Effects on ability to drive and use machines

This may be severely affected during and after treatment with Methadone as it may cause drowsiness and reduce alertness. The time after which such activities may be safely resumed is extremely patient dependant and must be decided by the physician.

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 adverse effects of methadone are generally the same as with other opioids, most commonly nausea and vomiting, which are observed in approximately 20% of the patients who undergo methadone out-patient treatment, where the medicinal control is often unsatisfactory.

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

Adverse reactions listed below are classified according to frequency and system organ class. These reactions are more frequently observed in non-opioid-tolerant individuals. Frequency groupings are defined according to the following convention: very common (≥ 1/10), common (≥ 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, hypoglycaemia
Psychiatric disorders	Common	Euphoria, hallucinations
	Uncommon	Dysphoria, dependence, agitation, insomnia, disorientation, reduced libido
	Not known	Drug dependence (see section 4.4)
Nervous system disorders	Common	Sedation
	Uncommon	Headache, syncope

Eye disorders	Common	Blurred vision, miosis, dry eyes
	Not known	Nystagmus, Strabismus, visual acuity reduced
Ear and labyrinth disorders	Common	Vertigo
Cardiac disorders	Rare	Bradycardia, palpitations, cases of prolonged QT interval and torsade de pointes have been reported, especially with high doses of methadone.
Vascular disorders	Uncommon	Facial flush, hypotension
Respiratory, thoracic and mediastinal disorders	Uncommon	Pulmonary oedema, exacerbation of asthma, dry nose, respiratory depression particularly with large doses,
	Not known	Central sleep apnoea syndrome
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	Raised prolactin levels with long-term administration Hypoadrenalism, Hypogonadism,
Renal and urinary disorders	Uncommon	Urinary retention, anti-diuretic effect
Reproductive system and breast disorders	Uncommon	Reduced potency, galactorrhoea, dysmenorrhoea and amenorrhoea
General disorders and administration site conditions	Common	Fatigue, drowsiness
	Uncommon	Oedema of the lower extremities, asthenia, oedema, hypothermia, drug withdrawal syndrome
Investigations	Common	Weight increase

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 the Yellow Card Scheme at www.mhra.gov.uk/yellowcard or search for the MHRA Yellow Card in the Google Play or Apple App Store.

4.9. Overdose

Patients should be informed of the signs and symptoms of overdose and to ensure that family and friends are also aware of these signs and to seek immediate medical help if they occur.

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, apnea, circulatory collapse, cardiac arrest and death may occur. Hypoglycaemia has been reported. Toxic leukoencephalopathy has been observed with methadone overdose.

Treatment: A patent airway and assisted or controlled ventilation must be assured. Narcotic antagonists may be required, but it should be remembered that Methadone is a long-acting depressant (36-48 hours) whereas antagonists act for 1-3 hours, so that treatment with the latter must be repeated as needed. Observation and supportive measures must be continued for 36-48 hours. 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: N07BC02

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 1-

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 K 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 pA_2 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

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. With an intramuscular dose of 10mg, a peak plasma concentration of 75µg per litre 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 levels occur in dependent persons on a stable dose of oral Methadone, without any relation to symptoms. Methadone is secreted into sweat and found in saliva and in high concentration in gastric juice. The concentration in cord blood is about half the maternal level.

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. 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.

5.3. Preclinical safety data

Not applicable

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sucrose, propylene glycol, methyl hydroxybenzoate, propyl hydroxybenzoate, liquid maltitol, tartrazine E102, sunset yellow E110, patent blue V E131, poloxamer 188, simethicone emulsion 30% and purified water.

6.2. Incompatibilities

No major incompatibilities are known

6.3. Shelf life

Amber (type III) glass bottle: 2 years

6.4. Special precautions for storage

Store below 25°C but not in a refrigerator, protected from light, under secure conditions as per the Controlled Drugs Regulations.

6.5. Nature and contents of container

Glass bottle pack

Bottle:	Amber (type III) glass
Capacities:	100ml or 500ml.
Closure:	HDPE, child resistant, tamper evident, EPE wadded closure

Not all pack sizes may be marketed.

6.6. Instruction for use, handling and disposal

None stated

7 MARKETING AUTHORISATION HOLDER

Rosemont Pharmaceuticals Ltd
Rosemont House
Yorkdale Industrial Park
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