

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Phymet DTF 1 mg/ml Syrup

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains methadone hydrochloride 1mg.

Excipients with known effect:

Sunset Yellow (E110) 0.0125 mg per ml

Brilliant blue (E133) 0.0050 mg per ml

Methyl para-hydroxybenzoate (E218) 1.0 mg per ml

Sodium benzoate (E211) 1.0 mg per ml

Glycerol 110 mg per ml

Ethanol 2.0 mg per ml

Maltitol 325 mg per ml

Sorbitol 52 mg per ml

For the full list of excipients see section 6.1

3 PHARMACEUTICAL FORM

Syrup.

Clear, green oral solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Phymet DTF Syrup 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.

Phymet DTF Syrup is indicated in adults 18 years and older.

Consideration should be given to official guidance on the appropriate use of Opioid Substitution Treatment.

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. In absence of adequate pain control, the possibility of hyperalgesia, tolerance and progression of underlying disease should be considered (see section 4.4).

Phymet DTF Syrup 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 and 120 mg, until there are no signs of withdrawal or intoxication. After stabilisation, the dose of methadone is gradually decreased 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

Phymet DTF Syrup is not recommended for use in this age group, since documented clinical experience has been insufficient to establish a suitable dosage regimen; furthermore, children are particularly sensitive to the respiratory and central nervous system depressant effects of methadone (see section 4.4).

Elderly people

Phymet DTF Syrup has a long plasma half life which may lead to accumulation, particularly if renal function is impaired (see section 4.4 and section 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).

Renal impairment

Phymet DTF Syrup 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.

Hepatic impairment

Particular care should be taken when Phymet DTF Syrup is to be used in patients with hepatic impairment as these patients metabolise methadone more slowly than normal patients. Where not contraindicated, Phymet DTF Syrup 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).

Cardiac repolarisation disorders

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 Phymet DTF Syrup, 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

Phymet DTF Syrup is contra-indicated in patients:

- who are hypersensitive to methadone or any of the excipients.
- with respiratory depression, especially in the presence of cyanosis, obstructive airways disease and excessive bronchial secretions.
- during an attack of bronchial asthma.
- with acute alcoholism, head injury and raised intracranial pressure (pupillary response affected).
- Phaeochromocytoma
- receiving monoamine oxidase inhibitors (MAOIs) or within 14 days of stopping such treatment (see section 4.5).

- with ulcerative colitis, since it may precipitate toxic dilatation 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).
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- Patients dependent on non-opioid drugs.
 - Risk of paralytic ileus (including drug induced gastrointestinal hypotonia).

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.

Caution should be exercised in patients with hepatic dysfunction or renal dysfunction (see section 4.2).

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

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.

Hepatobiliary disorders

Methadone may cause dysfunction and spasm of the sphincter of Oddi, increasing the risk of biliary tract symptoms and pancreatitis. Therefore, methadone has to be administered with caution in patients with pancreatitis and diseases of the biliary tract.

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. It may exacerbate asthma due to histamine release (see section 4.2).

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 arrhythmogenic 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.

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.

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 Phymet DTF Syrup 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 Phymet DTF Syrup 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. The clinical need for continuing treatment should be reviewed regularly in all patients.

Abuse or intentional misuse of Phymet DTF Syrup may result in overdose and/or death. It is important that patients only use medicines that are prescribed for them at the dose they have been prescribed and do not give this medicine to anyone else.

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). Additional support and monitoring may be necessary when prescribing for patients at risk of opioid misuse.

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.

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

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.

Drug withdrawal syndrome

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 (see section 4.8).

Hyperalgesia

As with other opioids, in case of insufficient pain control in response to an increased dose of methadone, the possibility of opioid-induced hyperalgesia should be considered. 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. A dose reduction or treatment review may be indicated.

Other

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

- hypothyroidism
- hypopituitarism
- prostatic hypertrophy
- shock

- hypotension
- inflammatory or obstructive bowel disorders
- myasthenia gravis

Opioids and CNS depressants

Concomitant treatment with other agents with CNS depressant activity is not advised due to the potential for CNS and respiratory depression. Concomitant treatment with opioids and CNS depressants (including benzodiazepines, barbiturates and antipsychotics) should only be used when alternative treatment options are inadequate (see section 4.5). Respiratory depression, sedation, coma and death can occur if opioids are used with benzodiazepines, alcohol or other CNS depressants. Patients should be monitored closely for respiratory depression and sedation. Dosage and duration of treatment should be limited to the minimum to achieve desired clinical effect, if a decision is made to prescribe methadone concomitantly with sedative medicines. In this respect, it is strongly recommended to inform patients and their caregivers to be aware of these symptoms (see section 4.5).

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

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

Presentation of adrenal insufficiency may include nonspecific symptoms and signs, including nausea, vomiting, anorexia, fatigue, weakness, dizziness and 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 physiologic replacement doses of corticosteroids and opioid should be withdrawn to allow adrenal function to recover.

Decreased sex hormones and increased prolactin

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

Excipients

Phymet DTF contains maltitol and sorbitol as maltitol solution, which may have a mild laxative effect. Maltitol has a calorific value of 2.3 kcal/g and sorbitol has a calorific value of 2.6 kcal/g. Patients with rare hereditary problems of fructose intolerance (HFI) should not be given this medicine.

Phymet DTF contains glycerol which may cause headache, stomach upset and diarrhoea.

Phymet DTF contains 1 mg sodium benzoate in each ml.

This medicine also contains small amounts of ethanol (alcohol), approximately 2mg/ml. The small amount of alcohol in this medicine will not have any noticeable effects.

This medicine contains sunset yellow (E110) and brilliant blue (E133) which may cause allergic reactions and methyl para-hydroxybenzoate (E218) which may cause allergic reactions (possibly delayed).

This medicine contains less than 1 mmol sodium (23 mg) per a maximum daily dose of 120 ml, that is to say essentially 'sodium-free'.

Grapefruit juice

Grapefruit juice increases the bioavailability of methadone due to decreased methadone metabolism (see section 4.5).

Paediatric population

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 18 years of age. 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 (see section 4.2).

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. Babies born to mothers receiving methadone may suffer withdrawal symptoms.

Endocrinopathies

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

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)

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, phenobarbital, carbamazepine, primidone, St John's Wort, and antiretroviral agents used in the treatment of HIV infection (particularly nevirapine, efavirenz and some protease inhibitors) and St John's Wort may decrease plasma concentrations of methadone. This has the potential to result in withdrawal symptoms. Adjustment of the dose of methadone should be considered. Methadone maintained patients beginning antiretroviral therapy should be monitored for evidence of withdrawal and methadone dose should be adjusted accordingly.

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.

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.

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).

Cyclizine and other sedating antihistamines

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

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

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.

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.

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.

Erythromycin

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

Fluconazole, voriconazole and ketoconazole

Fluconazole, voriconazole and ketoconazole may raise methadone levels, due to decreased methadone metabolism.

Depressant effects

The general depressant effects of methadone may be enhanced by other centrally-acting agents such as, alcohol, anaesthetics, hypnotics (including benzodiazepines, chloral hydrate and chlormethiazole), anxiolytics, sedatives, barbiturates, neuromuscular blocking agents, phenothiazines, tricyclic antidepressants, and tranquillisers e.g. benzodiazepines.

Some psychotropic drugs, however, may potentiate the analgesic effects of methadone (see section 4.4).

Concomitant treatment with opioids and CNS depressants should only be used when alternative treatment options are inadequate (see section 4.4). 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).

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.

Serotonergic drugs

Serotonin syndrome (including altered mental status, autonomic instability, neuromuscular abnormalities, and/or gastrointestinal symptoms) has been reported following concomitant treatment with opioids (pethidine), serotonergic drugs such as Selective Serotonin Re-uptake Inhibitor (SSRI), Serotonin Norepinephrine Re-uptake Inhibitor (SNRI) and tricyclic antidepressants (TCAs) and MAOIs (see section 4.4).

Drugs affecting gastrointestinal activity

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

Pregnancy Tests:

Methadone may interfere with the urine testing for pregnancy.

pH of urine

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

Opioid Agonist Analgesics:

Additive CNS depression, respiratory depression and hypotension

Opioid antagonists:

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

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.

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.

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).

4.6 Fertility, pregnancy and lactationFertility

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 including respiratory depression, low birth weight, neonatal withdrawal syndrome and increased rate of stillbirths (see section 5.3).

Some observational studies have reported congenital malformations and neurodevelopmental impairment in children born to women treated with methadone for opioid use disorder during pregnancy. However, due to study limitations and confounding by maternal, familial and socioenvironmental factors associated with opioid use disorders no conclusions can be drawn regarding the contribution of methadone.

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.

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 4.3). During labour there is a risk of gastric stasis and inhalation pneumonia in the mother and foetal distress.

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).

Breastfeeding

Methadone is excreted 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 low, 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

Phymet has moderate influence on the ability to drive and use machines. In common with other opioids, Phymet DTF Syrup may produce orthostatic hypotension, 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. 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 $\geq 1/10$

Common $\geq 1/100$ to $< 1/10$

Uncommon $\geq 1/1,000$ to $< 1/100$

Rare $\geq 1/10,000$ to $< 1/1,000$

Very rare $\leq 1/10,000$

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.

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: hypoglycaemia, anorexia, hypokalaemia, hypomagnesaemia.

Psychiatric disorders

Common: confusion, euphoria, hallucinations.

Uncommon: dysphoria, dependence, agitation, insomnia, disorientation, reduced libido.

Not known: drug dependence

Endocrine disorders

Not known: adrenal insufficiency (see section 4.4), raised prolactin levels with long-term administration, hypoadrenalism, hypogonadism.

Nervous system disorders

Very common: dizziness#, drowsiness#, light-headedness#.

Uncommon: headache, syncope.

Not known: serotonin syndrome (see section 4.4).

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, 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

Uncommon: facial flush, hypotension.

Rare: collapse.

Respiratory, thoracic and mediastinal disorders

Uncommon: pulmonary oedema, exacerbation of asthma, dry nose, respiratory depression (see section 4.4).

Not known: central sleep apnoea syndrome

Gastrointestinal disorders

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

Uncommon: glossitis, acute pancreatitis

Hepatobiliary disorders

Not known: Methadone, in common with other opioids may cause spasm of the biliary tract (see section 4.3), sphincter of Oddi dysfunction

Skin and subcutaneous tissue disorders

Common: transient rash, sweating.

Uncommon: pruritis, urticaria, other rash and in very uncommon cases bleeding urticaria.

General disorders and administration site conditions

Uncommon: oedema of the lower extremities, asthenia, oedema, hypothermia, drug withdrawal syndrome*.

Investigations

Common: weight increase.

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

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, apnoea, circulatory collapse, cardiac arrest, coma and death may occur.

Hypoglycaemia has been reported.

Toxic leukoencephalopathy has been observed with methadone overdose.

Treatment

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

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. 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.

Patients should be monitored closely for at least 48 h 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

Drugs used in opioid dependence.

ATC Code: N07 BC02

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 periaqueductal 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-diphenylpyrrolidine (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 *invitro* 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

Glycerol
Methyl para-hydroxybenzoate (E218)
Sodium benzoate (E211)
Maltitol solution (contains Sorbitol)
Flavour spice IFF 17.40.1831 (contains Ethanol)
Sunset yellow (E110)
Brilliant blue (E133)
Purified water

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

Amber glass bottle with a child resistant polypropylene cap with LDPE-PVDC-LDPE faced wads.

Pack size: 500ml

6.6 Special precautions for disposal

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

7 MARKETING AUTHORISATION HOLDER

GlaxoSmithKline (Ireland) Limited
12 Riverwalk
Citywest Business Campus
Dublin 24
Ireland

8 MARKETING AUTHORISATION NUMBER

PA1077/074/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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Date of last renewal: 13 July 2008

10 DATE OF REVISION OF THE TEXT

September 2026