SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Physeptone 1mg /ml oral solution sugar-free

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains methadone hydrochloride 1mg.

Excipients with known effect
Contains excipients Liquid Maltitol (E 965) 0.4 ml/ml and Sunset Yellow (E110) 0.008 mg/ml.

For the full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Oral solution

A clear, green oral solution

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

The treatment of opioid drug addiction as a narcotic abstinence syndrome suppressant.

4.2 Posology and method of administration

Prior to starting treatment with opioids, a discussion should be held with patients to put in place a strategy for ending treatment with methadone in order to minimise the risk of addiction and drug withdrawal syndrome (see section 4.4). 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).

Posology

The dose is adjusted according to the degree of dependence with the aim of gradual reduction.

Adults
Initially 10 – 2 0mg per day, increasing by 10 - 20mg daily until there is no sign of withdrawal or intoxication. The usual dose is 40-60 mg per day.

Elderly
In the case of the elderly or ill patients, repeated doses should be given with extreme caution.
Paediatric population
Not recommended (see section 4.3)

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.

Method of administration
For oral use only.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Respiratory depression, obstructive airways disease and during an acute asthma attack
- Acute alcoholism (See section 4.5)
- Head injury and raised intracranial pressure (further rise in intracranial pressure – see section 4.8: papillary response affected)
- Concurrent administration of MAOI drugs, including moclobemide, or for 2 weeks after stopping (See section 4.5)
- Use during labour (prolonged duration of action increases the risk of neonatal depression)
- Children (serious risk of toxicity)
- Patients with ulcerative colitis, since methadone may precipitate toxic dilation or spasm of the colon.
- Patients dependent on non-opioid drugs
- 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

In the case of elderly or ill patients, repeated doses should only be given with extreme caution. Methadone is a drug of addiction and is controlled under the Misuse of Drugs Act 1971 (Schedule 2). Methadone 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 possibly death.

Tolerance and dependence of the morphine type may occur. Methadone can produce drowsiness and reduce consciousness although tolerance to these effects can occur after repeated use. Methadone should be given with caution to patients with history of asthma (see section 4.3), convulsive disorders, depressed respiratory reserve, hypotension, shock, prostatic hyperplasia, adrenocortical insufficiency, inflammatory or obstructive bowel disorders, myasthenia gravis or hypothyroidism. 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 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 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 QTprolongation,

- concomitant treatment with drugs which may cause electrolyte abnormalities,

- concomitant treatment with cytochrome P450 CYP 3A4 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 100 mg/d and at seven days after titration.

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

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

Drug dependence, tolerance and potential for abuse

Prolonged use of this product may lead to drug dependence (addiction), even at therapeutic doses. The risks are increased in individuals with current or past history of substance misuse disorder (including alcohol misuse) or mental health disorder (e.g., major depression). Overuse or misuse 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. Patients

should be closely monitored for signs of misuse, abuse, or addiction. The clinical need for continuing opioid substitution therapy should be reviewed regularly.

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. The decision to maintain a patient on a longterm 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.

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. 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).

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)

Hepatic impairment

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.

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 16 (See sections 4.2, 5.2).

Excipient warnings:

This product contains Liquid maltitol (E965). Patients with rare hereditary problems of fructose intolerance should not take this medicine

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

Concomitant use of Physeptone 1mg /ml oral solution sugar-free 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 Physeptone 1mg /ml oral solution sugar-free 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).

4.5 Interaction with other medicinal products and other forms of interaction

CNS depressants:
Alcohol, anaesthetics, hypnotics and 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).

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

Histamine H2_Antagonists:

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

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.

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.

MAOI's:
The concurrent use of MAOl's is contraindicated (see 4.3 Contraindications) as they may prolong and enhance the respiratory depressant effects of methadone.

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 antagonise 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:
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.

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

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).

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

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

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.

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.

4.6 Fertility, pregnancy and lactation

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 birth weight; 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 birth weight but methadone has not convincingly been associated with congenital malformations. It should not be used during labour, see "contraindications"

Lactation:
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

The ability to drive or operate machinery may be severely affected during and after treatment with methadone. The time after which such activities can be safely resumed is extremely patient dependent 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

Endocrine Disorders
Hyperprolactinaemia.

Psychiatric disorders
Confusion particularity at the start of the treatment can occur

Changes of mood, including euphoria, and hallucinations are occasionally reported. Drug dependence (see section 4.4).

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

Eye Disorders
Miosis, dry eyes

Ear and labyrinth disorders
Vertigo.

Cardiac Disorders
Bradycardia and palpitations can occur. Cases of QT prolongation and torsades de pointes have been rarely reported.

Vascular disorders
Orthostatic hypotension, facial flushing.

Respiratory, thoracic and mediastinal disorders
Exacerbation of existing asthma, dry nose, respiratory depression particularly with larger doses.

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

Skin and subcutaneous tissue disorders
Rashes. Long-term administration may produce excessive sweating

Renal and urinarv disorders
Less commonly micturition difficulties are observed.

Metabolism and nutrition disorders SOC
Hypoglycaemia.

Reproductive system and breast disorders
Galactorrhoea, dysmenorrhoea, amenorrhoea

General disorders
Hypothermia, drug withdrawal syndrome.

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 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.

Management

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/kg) or Levallorphan (0.02mg/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 race mate 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 pA2 value similar to its 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 10 mg, a peak plasma concentration of 75 µg per litre is reached in one hour. With regular oral doses of 100-120 mg daily, plasma concentrations rise from trough levels of approximately 500 µg/L to a peak of about 900 µg/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.

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.

5.3 Preclinical safety data

There are no preclinical data of relevance to the prescriber, which are additional to those already included in other sections of the SmPC.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Liquid maltitol (E965),
Sodium Benzoate (E211),
Green S (E142),
Sunset Yellow (E110),
Quinoline Yellow (E104),
Hydrochloric acid (for pH-adjustment)
Purified Water.

6.2 Incompatibilities

Not applicable

6.3 Shelf life

2 years

Use within 28 days of opening

6.4 Special precautions for storage

Do not Store above 25°C.

6.5 Nature and contents of container

30ml, 50ml, 100ml and 500ml of the oral solution in Type III amber glass bottles fitted with child resistant closures. Contact material: Polypropylene.

500ml and 1L HDPE bottle with tamper evident and child resistant cap. The material of construction of the closure is HDPE with an EP wad.

2.5L and 5L bottle with tamper evident cap or tamper evidence will be provided with a tamper evident seal. The material of construction of the closures is HDPE with an EP wad.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused product or waste material should be returned to the pharmacy or doctor for disposal.

7 MARKETING AUTHORISATION HOLDER

Martindale Pharmaceuticals Ltd
Bampton Road, Harold Hill, Romford, RM3 8UG, U.K.

8 MARKETING AUTHORISATION NUMBER(S)

PL 00156/0320

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 3rd June 2009

10 DATE OF REVISION OF THE TEXT

11/11/2021