

# Summary of Product Characteristics

## 1 NAME OF THE MEDICINAL PRODUCT

Methadone Teva 1 mg/ml Oral solution

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One millilitre of oral solution contains 1 mg of methadone hydrochloride.

### Excipients

One millilitre of oral solution contains 1.2 mg methyl parahydroxybenzoate, 0.3 mg propyl parahydroxybenzoate and 300 mg of maltitol liquid.

For a full list of excipients, see section 6.1.

## 3 PHARMACEUTICAL FORM

Oral solution

Clear, green liquid

## 4 CLINICAL PARTICULARS

### 4.1 Therapeutic Indications

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

Local guidance on the management of opioid addiction should be followed.

### 4.2 Posology and method of administration

For oral administration only.

Local guidance may differ from the posology described hereafter and should be followed.

Methadone should preferably be prescribed in special treatment institutions in view of the great risks that such treatment involves. In cases where this is not possible, contact should be made with the nearest drugs advice centre.

### Addiction

#### *Adults*

Initially 10-20 mg per day. A supplementary dose on the same day may be considered when there is evidence of persistent opioid withdrawal provided that the person has been fully assessed by a clinician with appropriate skills and experience. The dose should be increased by 10 mg per day until there are no signs of withdrawal or intoxication. The usual dose is 60-100 mg per day. The dose is adjusted according to the degree of dependence with the aim of gradual reduction at a speed dependent on the individual person *e.g.* 3% per week.

#### *Elderly*

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

#### *Children*

Not recommended for children.

### 4.3 Contraindications

- Hypersensitivity to methadone or to any of the excipients
- Respiratory depression
- Obstructive airways disease
- Raised intracranial pressure or head injury
- Concurrent administration with monoamine oxidase (MAO) inhibitors or within 2 weeks of discontinuation of treatment with them
- Absence of dependence on opioid substances

Use during labour is not recommended, the prolonged duration of action increases the risk of neonatal depression.

This medicinal product is not suitable for paediatric use.

### 4.4 Special warnings and precautions for use

Caution should be exercised in patients with hepatic dysfunction or renal dysfunction, hypothyroidism or prostatic hypertrophy.

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

#### Addiction/tolerance/dependence

Methadone is 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.

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

#### Withdrawal

Abrupt cessation of treatment can lead to withdrawal symptoms which, although similar to those with morphine, are less intense but more prolonged. Withdrawal of treatment should therefore be gradual.

#### Respiratory depression

Due to the slow accumulation of methadone in the tissues, respiratory depression may not be fully apparent for a week or two and may exacerbate asthma due to histamine release.

Use during an asthma attack is not recommended.

#### Hepatic disorders

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

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

#### Neonates/children

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

Further warnings

Babies born to mothers receiving methadone may suffer withdrawal symptoms.

Methadone should be used with great caution in patients with acute alcoholism, convulsive disorders and head injuries.

Methadone has the potential to increase intracranial pressure especially where it is already raised.

Methadone should be used with caution in patients with hypothyroidism, adrenocortical insufficiency, prostatic hyperplasia, hypotension, shock, inflammatory or obstructive bowel disorders or myasthenia gravis.

Cases of QT interval prolongation and *torsades de pointes* have been reported during treatment with methadone, particularly at high doses (>100 mg/day). 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 or ischaemic heart disease,
- liver disease,
- family history of sudden death,
- electrolyte abnormalities, *i.e.* hypokalaemia, hypomagnesaemia
- concomitant treatment with substances that have a potential for QT-prolongation,
- concomitant treatment with substances 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 substances 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/day and at seven days after titration.

Caution should be exercised in patients who are concurrently taking central nervous system (CNS) depressants.

Excipients

This medicinal product contains parahydroxybenzoates and may cause allergic reactions (possibly delayed).

This medicinal product contains maltitol liquid: patients with rare hereditary problems of fructose intolerance should not take this medicinal product.

**4.5 Interaction with other medicinal products and other forms of interaction**MAO inhibitors

The concurrent use of MAO inhibitors is contraindicated (see section 4.3) as they may prolong and enhance the respiratory depressant effects of methadone.

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 section 4.4).

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

## Histamine H<sub>2</sub>- antagonists

Histamine H<sub>2</sub> 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 such as phenytoin, phenobarbital, carbamazepine and primidone

Anticonvulsants induce methadone metabolism with the risk of precipitating withdrawal syndrome. Adjustment of the dose of methadone should be considered.

### 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

These agents have 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). 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 the methadone dose should be adjusted accordingly.

### Ciprofloxacin

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

### Other agents

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

### Pregnancy tests

Methadone may interfere with urine testing for pregnancy.

### Cytochrome P450 3A4 inhibitors

Methadone clearance is decreased when co-administered with substances which inhibit CYP3A4 activity, such as some anti-human immunodeficiency (HIV) agents, macrolide antibiotics, cimetidine and azole antifungal agents (since the metabolism of methadone is mediated by the CYP3A4 isoenzyme).

St. John's Wort

St. John's Wort may lower plasma concentrations of methadone.

In patients taking agents affecting cardiac conduction, or substances which may affect electrolyte balance there is a risk of cardiac events when methadone is taken concurrently.

**4.6 Fertility, pregnancy and lactation**

Pregnancy

Limited data on the use of methadone in pregnancy in humans show no elevated risk of congenital abnormalities. Withdrawal symptoms / respiratory depression may occur in neonates of mothers who were treated with methadone chronically during pregnancy. Data from animal studies have shown reproduction toxicity (see section 5.3). It is generally advisable not to detoxify the patient, especially after the 20<sup>th</sup> week of pregnancy, but to administer maintenance treatment with methadone. The use of methadone oral solution just before and during birth is advised against because of the risk of neonatal respiratory depression.

Lactation

Methadone is excreted in breast milk and the average milk/plasma ratio is 0.8. Breast-feeding may be given on doses of up to 20 mg per day. At higher doses the benefits of breast-feeding must be weighed against the possible adverse effects on the infant.

**4.7 Effects on ability to drive and use machines**

Methadone has major influence on the ability to drive and use machines, during and after treatment, as it may cause drowsiness and reduce alertness. The time after which such activities may be safely resumed is extremely patient-dependent and must be decided by the physician.

**4.8 Undesirable effects**

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 ( $\geq 1/10$ ), 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 ( $< 1/10,000$ ), 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
	Unknown	Anorexia
	Not known	Hypokalaemia, hypomagnesaemia

Psychiatric disorders	Common	Euphoria, hallucinations
	Uncommon	Dysphoria, agitation, insomnia, disorientation, reduced libido
Nervous system disorders	Common	Sedation
	Uncommon	Headache, syncope
Eye disorders	Common	Blurred vision, miosis
Ear and labyrinth disorders	Common	Vertigo
Cardiac disorders	Rare	Bradycardia, palpitations, cases of prolonged QT interval and <i>torsade de pointes</i> have been reported, especially with high doses of methadone.
Vascular disorders	Uncommon	Facial flush, hypotension
Respiratory, thoracic and mediastinal disorders	Uncommon	Pulmonary oedema, respiratory depression
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	Pruritus, urticaria, other rash and in very uncommon cases bleeding urticaria
Renal and urinary disorders	Uncommon	Urinary retention, anti-diuretic effect
Reproductive system and breast disorders	Uncommon	Reduced potency and amenorrhoea
General disorders and administration site conditions	Common	Fatigue
	Uncommon	Oedema of the lower extremities, asthenia, oedema
Investigations	Common	Weight increase

4.9 Overdose

Symptoms

Serious overdose 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 overdose, particularly by the intravenous route, apnoea, circulatory collapse, cardiac arrest and death may occur.

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 to 48 hours), whereas antagonists act for 1 to 3 hours, so that treatment with the latter must be repeated as needed. An antagonist should not be administered, however, in the absence of clinically significant respiratory or cardiovascular depression. The administration of naloxone is advised.

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

Pharmacotherapeutic group: Drugs used in opioid dependence  
ATC code: N07B C02

Methadone is a strong opioid agonist with actions predominantly at the  $\mu$  receptor. The analgesic activity of the racemate is almost entirely due to the *l*-isomer, which is at least 10 times more potent as an analgesic than the *d*-isomer. The *d*-isomer lacks significant respiratory depressant activity but does have anti-tussive effects. Methadone also has some agonist actions at the  $\kappa$  and  $\delta$  opiate receptors.

These actions result in analgesia, depression of respiration, suppression of cough, nausea and vomiting (*via* an effect of 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 substances, 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 gastrointestinal tract, but undergoes fairly extensive first-pass metabolism.

With an intramuscular dose of 10 mg, a peak plasma level of 75  $\mu\text{g/L}$  is reached in one hour. With regular oral doses of 100-120 mg daily, plasma concentrations rise from trough levels of approximately 500  $\mu\text{g/L}$  to a peak of about 900  $\mu\text{g/L}$  in 4 hours. Marked variations in plasma levels occur in dependent persons on a stable dose of oral methadone, without any relation to symptoms.

#### Distribution

Methadone is bound to albumin and other plasma proteins and to tissue proteins (probably lipoproteins), the concentrations in the 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. Methadone is secreted in sweat and found in saliva and in high concentrations in gastric juice. The concentration in cord blood is about half the maternal level.

#### Metabolism

The metabolism of methadone is catalysed primarily by CYP3A4, but CYP2D6 and CYP2B6 are also involved, to a smaller extent. Metabolism is mainly *N*-demethylation, which produces the most important metabolites: 2-ethylidine, 1,5-dimethyl-3,3-diphenylpyrrolidine (EDDP) and 2-ethyl-5-methyl-3,3-diphenyl-1-pyrrolidine (EMDP), which are both inactive. Hydroxylation to methanol followed by *N*-demethylation to normethadol also occurs to some extent. Other metabolic reactions also occur, and at least eight other metabolites are known.

#### Elimination

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 hours (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 life of elimination.

### Special populations

There are no significant differences in the pharmacokinetics between men and women. The clearance of methadone is decreased only to some extent in the elderly (>65 years).

## **5.3 Preclinical safety data**

Methadone at high doses caused birth abnormalities in marmots, hamsters and mice, in which most reports were of exencephaly and defects in the central nervous system. Rachischisis in the cervical region was found occasionally in mice. Non-closure of the neural tube was found in chicken embryos. Methadone was not teratogenic in rats and rabbits. Also a reduced number of young was found in rats and increased mortality, growth retardation, neurological behavioural effects and reduced brain weight were found in the pups. Reduced ossification of the digits, sternum and skull was found in mice and a smaller number of fetuses per litter. No carcinogenicity studies have been carried out.

## **6 PHARMACEUTICAL PARTICULARS**

### **6.1 List of excipients**

Methyl parahydroxybenzoate (E218)  
Propyl parahydroxybenzoate (E216)  
Propylene glycol (E1520)  
Maltitol, liquid (E965)  
Caramel colour (E150d)  
Patent blue 85 (E131)  
Purified water

### **6.2 Incompatibilities**

None known

### **6.3 Shelf life**

2 years  
Shelf-life after first opening: 50 days

### **6.4 Special precautions for storage**

Do not freeze.  
Keep the bottle tightly closed.

### **6.5 Nature and contents of container**

Amber glass bottles with White/yellow plastic child-resistant tamper evident polypropylene closures  
Pack sizes: 30, 50, 100 or 500 ml.  
Not all pack sizes may be marketed.



## **6.6 Special precautions for disposal and other handling**

Brown precipitate may appear in the bottle that does not affect quality of the product. The precipitate dissolves after shaking of the bottle.

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

## **7 MARKETING AUTHORISATION HOLDER**

Teva Pharma B.V.  
Swensweg 5,  
2031 GA Haarlem,  
The Netherlands

## **8 MARKETING AUTHORISATION NUMBER**

PA 749/116/1

## **9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

Date of first authorisation: 19th August 2011

## **10 DATE OF REVISION OF THE TEXT**

October 2015