EPTADONE 1MG/ML ORAL SOLUTION
(METHADONE HYDROCHLORIDE)
PL 20985/0001-4

EPTADONE 5MG/ML ORAL SOLUTION
(METHADONE HYDROCHLORIDE)
PL 20985/0005-6

UKPAR

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EPTADONE ORAL SOLUTION (METHADONE HYDROCHLORIDE)

PL 20985/0001-6

LAY SUMMARY

The MHRA granted Regulatory Pharma Net s.r.l. Marketing Authorisations (licences) on the 13th April 2006, for Eptadone 1mg/ml Oral Solution (PL 18813/0001-4) and Eptadone 5mg/ml Oral Solution (PL 18813/0005-6). These Prescription Only Medicines (POM), available on special prescription, are used to treat opioid drug addiction and to control pain.

Eptadone Oral Solution contains the active ingredient methadone hydrochloride which is an opioid drug substitute and has analgesic effects.

The applicant has supplied scientific literature to demonstrate that the active substance in Eptadone Oral Solution has been in well-established medicinal use within the European Community, with acceptable levels of effectiveness and safety.

No new or unexpected safety concerns arose from these applications. It was therefore judged that the benefits of taking Eptadone Oral Solution outweigh the risks. Hence Marketing Authorisations have been granted.
EPTADONE ORAL SOLUTION (METHADONE HYDROCHLORIDE)

PL 20985/0001-6

SCIENTIFIC DISCUSSION

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INTRODUCTION

Based on the review of the data on quality, safety and efficacy the UK granted marketing authorisations for Eptadone Oral Solution to Regulatory Pharma Net srl. on 13th April 2006. The products are Prescription Only Medicines (POM), available on special prescription.

The applications were submitted as ‘bibliographic applications’, under article 10(a) [formerly 10.1 (a) (ii)] of Directive 2001/83/EC. The scientific literature demonstrated that the active substance in Eptadone Oral Solution has been in well-established medicinal use within the European Community, with acceptable efficacy and safety.

The product contains the active ingredient methadone hydrochloride and is indicated in the treatment of moderate to severe pain or in the treatment of opioid drug addiction (as a narcotic abstinence syndrome suppressant).

Methadone is a strong opioid agonist with actions predominantly at the µ receptor. The analgesic activity of the racemate is almost entirely due to the l-isomer, which is at least 10 times more potent as an analgesic than the d-isomer.
1. **INTRODUCTION**

These national standard abridged applications are for oral solutions containing 1mg/ml methadone hydrochloride in bottles containing 20ml, 40ml and 60ml (single dose) and 100ml and 1000ml (multidose) solutions. In addition, applications have been submitted for solutions containing 5mg/ml methadone hydrochloride in a 20ml single dose and 1000ml multidose container. The applicant has proposed that the products are indicated for treatment of opioid drug addictions (as a narcotic abstinence syndrome suppressant). They are also proposed for use as an analgesic for moderate to severe pain.

These applications have been made as bibliographic applications under Article 10(a) [formerly 10.1(a)(ii)] of Directive 2001/83/EC.

2. **COMMON TECHNICAL DOCUMENT SUMMARIES**

2.1 **INTRODUCTION**

A satisfactory introduction has been provided.

2.2 **QUALITY OVERALL SUMMARY (QOS)**

A satisfactory Quality Overall Summary has been provided.

3. **ACTIVE SUBSTANCE**

3.1 **GENERAL INFORMATION**

3.1.1 Nomenclature

pINNM: methadone hydrochloride

Chemical names:
(R,S)-6-Dimethylamino-4,4-diphenyl-3-heptanone hydrochloride
1,1-Diphenyl-1-(2-dimethylaminopropyl)-2-butanone hydrochloride

3.1.2 Structure

\[\text{C}_{21}\text{H}_{27}\text{NO.HCl} \quad \text{MW: 345.9 (hydrochloride), 309.5 (base)}\]

3.1.3 General Properties
White, odourless, bitter, crystalline powder, soluble in water, ethanol, isopropanol; practically insoluble in ether and glycerol. The substance melts at 233-236°C. The pH of a 1% solution is 4.5-6.5.

3.2 MANUFACTURE

3.2.1 Manufacturer

Two Active Ingredient Manufacturers (AIMs) have been proposed.

3.2.2 Manufacturing process description and process controls

Current, valid copies of Certificates of Suitability have been provided.

Details are covered by the two Certificates of Suitability.

3.2.3 Control of materials

A declaration has been provided from both AIMs confirming that no materials of animal or human origin are used in the manufacturing process.

Details are covered by the two Certificates of Suitability.

3.2.4 Controls of Critical Steps and Intermediates

Details are covered by the two Certificates of Suitability.

3.2.5 Process validation and/or valuation

Details are covered by the two Certificates of Suitability.

3.3 CHARACTERISATION

3.3.1 Elucidation of structure and other characteristics

The substance has a single asymmetric carbon atom, but is produced as the racemic mixture, as routinely confirmed through the specification by a test for optical rotation.

There is no evidence of polymorphism.

Details are covered by the two Certificates of Suitability.

3.3.2 Impurities
Details are covered by the two Certificates of Suitability.

3.4 CONTROL OF ACTIVE SUBSTANCE

3.4.1 Specification

Both sources of active substance comply with the current Ph Eur monograph for methadone hydrochloride.

The proposed specification is acceptable.

3.4.2 Analytical procedures / validation

The analytical methods are those described in the Ph Eur monograph, supplemented with validated in-house methods. The suitability of the methods will have been considered prior to issue of the Certificates of Suitability.

3.4.3 Batch analyses

Satisfactory batch data / Certificates of Analysis have been provided for batches of methadone hydrochloride manufactured by both AIMs. All batches comply with the proposed active substance specification.

3.4.4 Justification of specification

Covered by the two Certificates of Suitability.

3.5 REFERENCE STANDARDS OR MATERIALS

Details are covered by the two Certificates of Suitability.

3.6 CONTAINER CLOSURE SYSTEM

The AIMs use either polyethylene bags in fibre drums, polypropylene Securitainers with polyethylene lids or polyethylene bags in Securitainers, tins or drums.

Satisfactory specifications, certificates of analysis and food-contact declarations have been provided for the containers/closures used by the two named AIMs.

3.7 STABILITY

3.7.1 Stability summary and conclusions

It is known that methadone hydrochloride is sensitive to light.

No forced-degradation studies have been conducted. This is acceptable given that the active substance is well established.
Stability data has been provided by one AIM for batches of active substance manufactured at their proposed site. These batches have been stored in containers manufactured from materials as proposed for the commercial packs to simulate the bulk containers.

Stability data provided: RT (18-24°C), 35°C, 45°C, 25°C/60% & 40°C

Test parameters: Until April 1997: colour, assay (HPLC), impurities (TLC)  
From April 1997: assay (non-aq. titration), melting point, loss on drying, ordinary impurities (TLC)  
From July 2000: related substances (GLC)  
Current methods: description, assay (non-aq. titration), melting point, loss on drying, ordinary impurities (TLC, USP), related substances (TLC, Ph Eur/GLC, in-house)

Only minor changes were seen after storage under the above conditions. The finished product manufacturer has proposed a re-test period of 2 years. This is acceptable.

Stability data have also been provided by the alternative AIM for batches of active substance manufactured at their proposed site stored in glass vials with polyethylene shives and black Bakelite screw-caps with a polyethylene-faced wad, polyethylene liners in aluminium cans with a screw cap and in opaque polypropylene Securitainers with polyethylene lids.

Stability data provided: 25°C, 37°C

Test parameters: solution colour, changes in loss on drying / moisture, melting point, related substances (TLC and HPLC), optical rotation, solution pH and IR spectrum

Details of the analytical methods have been provided.

One batch produced an out of specification result, at one timepoint, for levels of individual impurities however the applicant considered this to be an atypical result. This is agreed.

In the absence of sufficient stability data to support a re-test period, the finished product manufacturer has committed to checking appearance, assay, related substances and loss on drying before use of a batch of active substance from this AIM. It is assumed that the acceptance criteria described in the active substance specification are applied. The results are valid for 30 days. This is acceptable.

Furthermore, it is stated that a stability study will be initiated in accordance with relevant guidelines.
3.7.2 Post-approval stability protocol and stability commitment

A commitment has been provided from both AIMs to continue on-going stability studies to the end of the proposed study period and to undertake new studies on batches of active substance, on an annual basis. Satisfactory protocol details have been provided.

4. MEDICINAL PRODUCT

4.1 DESCRIPTION AND COMPOSITION OF THE MEDICINAL PRODUCT

Table 1: Composition and function of ingredients

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Function</th>
<th>Reference Standard</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methadone hydrochloride</td>
<td>Active substance</td>
<td>Ph Eur</td>
</tr>
<tr>
<td>Sucrose</td>
<td>Sweetener</td>
<td>Ph Eur</td>
</tr>
<tr>
<td>Glycerol</td>
<td>Vehicle</td>
<td>Ph Eur</td>
</tr>
<tr>
<td>Sodium benzoate</td>
<td>Preservative</td>
<td>Ph Eur</td>
</tr>
<tr>
<td>Citric acid monohydrate</td>
<td>Acidifier</td>
<td>Ph Eur</td>
</tr>
<tr>
<td>Lemon flavour</td>
<td>Flavour</td>
<td>HSE</td>
</tr>
<tr>
<td>Purified water</td>
<td>Solvent</td>
<td>Ph Eur</td>
</tr>
</tbody>
</table>

No Genetically Modified Organisms are included in the product.

4.2 PHARMACEUTICAL DEVELOPMENT

4.2.1 Components of the medicinal product

The function and rationale for inclusion of each ingredient in the product has been described. The levels are acceptable. The product has been marketed in Italy since 1982 and hence it is not considered necessary by the applicant to conduct compatibility studies. This is acceptable.

4.2.2 Formulation development

The applicant has discussed the key considerations for this product.

4.2.3 Physicochemical and biological properties

A key parameter is the solubility of methadone hydrochloride in the vehicle. Studies have demonstrated that the active substance will be fully in solution in the product.

The product complies with Ph Eur 5.1.3 with respect to efficacy of antimicrobial preservation. The studies have demonstrated that the proposed specification limits for sodium benzoate are justified.
4.2.4 Manufacturing process development

A common manufacturing process is used for the two strengths.

4.2.5 Container and closure system

The container/closure systems are discussed in section 4.7 of this report.

Product-container/closure compatibility studies have been reported. Physical compatibility, seal integrity and compliance with migration limits for total migration, vinyl monomer and tin (EU Directive 90/128/EEC and Ph Eur) has been shown.

4.3 MANUFACTURE

4.3.1 Manufacturer(s)

A manufacturing authorisation has been provided for the proposed finished product manufacturer.

4.3.2 Batch formula

Satisfactory formulae have been provided for the manufacture of batches of the 1mg/ml formulation and the 5mg/ml product.

4.3.3 Description of manufacturing process and process controls

A flow chart of the manufacturing process has been provided.

4.3.4 Control of critical steps and intermediates

Satisfactory tests and acceptance criteria have been set for in-process testing.

4.3.5 Process validation and/or evaluation

A retrospective process validation has been conducted for manufacture of the bulk 1mg/ml solution and for filling into all container sizes. All data are satisfactory.

A prospective process validation has been conducted for manufacture of the bulk 5mg/ml solution. The data presented relate to the first three industrial batches manufactured. All data are satisfactory. A study is also planned on a larger batch size using the same protocol. The data on the filling of the 1mg/ml solution has been presented in lieu of data on the 5mg/ml solution.

4.4 CONTROL OF EXCIPIENTS

4.4.1 Specifications
All ingredients comply with relevant Ph Eur monographs with the exception of the lemon flavour that is controlled to an in-house specification and which complies with Directive 88/388/EEC.

Satisfactory specifications and Certificates of Analysis have been provided for all ingredients.

4.4.2 Excipients of human or animal origin

The MAA form indicates that no materials of animal or human origin are contained in or used in the manufacturing process for the proposed products.

4.5 CONTROL OF MEDICINAL PRODUCT

4.5.1 Specification

The proposed finished product specification has been provided. The products comply with the Ph Eur monograph *Liquid Preparations for Oral Use*.

The widening of the limits for density over shelf life is supported by the stability data.

The proposed shelf life limits for sodium benzoate are satisfactory.

4.5.2 Analytical procedures / validation of analytical procedures

The in-house HPLC methods for identification and assay of methadone hydrochloride and sodium benzoate, and the method for related substances have been suitably validated. The Ph Eur membrane filtration test is used in the assessment of microbial quality against category 3A; this is appropriate.

4.5.3 Batch analyses

Satisfactory Certificates of Analysis have been provided for 3 full scale batches of the 20ml, 40ml, 60ml, 100ml and 1000ml presentations of the 1mg/ml product. Batch data have also been provided for 3 batches of the 20ml and 1000ml presentations of the 5mg/ml product. All batches were manufactured at the site proposed for commercial manufacture and comply with the proposed specifications.

4.5.4 Characterisation of impurities

No individual impurities have been quantified at significant levels in the stability studies.

4.5.5 Justification of specifications
A justification for the specification has been provided.

4.6 REFERENCE STANDARDS OR MATERIALS

The primary reference standards for methadone hydrochloride and for sodium benzoate are provided by the manufacturer of the active substance or by the USP. The working reference standards are characterised against the primary reference standards. Satisfactory certificates of analysis have been provided for the working standards.

4.7 CONTAINER-CLOSURE SYSTEM

The products are presented in transparent amber non-plasticised PVC bottles with aluminium (20, 40, 60, 100ml) or polypropylene (1000ml) pilfer-proof screw caps fitted with a polyethylene (EPE) liner. The 20, 40, 60 and 100ml containers include a polypropylene cover-cap to provide child resistance. It has been proposed that product will be available in single dose containers of 20ml, 40ml and 60ml and in multidose containers of 100ml and 1000ml. This is acceptable.

The 1mg/ml multidose presentations are provided with a polypropylene measuring cup marked with 5, 10, 15, 20, 25 and 30ml graduations. The 5mg/ml multidose presentations are provided with a polypropylene measuring cup marked with 1, 2, 3, 4, 5 and 6ml graduations. The administration devices are CE-certified. Satisfactory copies of the certificates have been provided as issued by the assigned Notified Bodies. Satisfactory migration studies have been performed.

The containers comply with Ph Eur 3.1.10 Materials based on non-plasticised poly(vinyl chloride) for containers for non-injectable, aqueous solutions. Satisfactory analytical data have been provided for three batches of 25ml (20ml fill) single dose containers and 1000ml bottles.

The caps comply with Directives 90/128/EEC and 94/82/EEC with respect to their suitability for contact with food. It has been stated that the bottles comply with relevant EU directives with respect to suitability for food use, namely 2002/72/EC and 78/142/EC. Appropriate studies have been performed on the liner to demonstrate absence of migration.

The identity of the bottles and caps is confirmed on receipt. Satisfactory specifications, drawings and certificates of analysis have been provided for representative batches of the packaging components.

A copy of the test method and validation data has been provided for the NIR test performed to identify the PVC bottles.

Satisfactory specifications have been provided for the delivery devices, supported by representative certificates of analysis.

4.8 STABILITY
4.8.1 Stability summary and conclusion

Stability data were provided for 20ml, 100ml and 1000ml batches of the 1mg/ml presentation. In addition, stability data were provided for 20ml and 1000ml of the 5mg/ml presentation. All batches were manufactured at the proposed commercial site and packed in the proposed commercial packs. A bracketing design has been applied to the 20ml, 40ml, 60ml and 100ml presentations whereby the 40ml and 60ml presentations have not been studied. This is acceptable. The 1000ml container has been studied independently.

The analytical methods used were as described for routine batch release.

Stability data provided: 25°C/60%, 40°C/75% and 40°C/25%

Test parameters: appearance, pH, density, colour, uniformity of mass, water loss, identification and assay of methadone hydrochloride and sodium benzoate, related substances, microbial quality

Photostability studies were performed on the 1mg/ml and 5mg/ml presentations in accordance with CPMP/ICH/279/95. The study was conducted using glass tubes, amber 20ml, 100ml and 1000ml PVC bottles, with appropriate dark controls. Appearance of solution, colour, assay and chromatographic characteristics were studied. It has been demonstrated that the intended containers need to be protected from the effects of light, although the 1000ml container provides adequate protection, being of thicker construction. An appropriate statement has been included on the labelling.

An in-use stability study was performed on the 1mg/ml presentation in 100ml and 1000ml PVC bottles and on the 5mg/ml presentation in 1000ml PVC bottles, in accordance with CPMP/QWP/2570/98. Appearance, pH, density, colour, assay and identification of methadone and sodium benzoate, and microbial properties were studied. An in-use shelf life for the multidose containers of 12 months is justified.

A stability study has been performed on the 1mg/ml presentation in 20ml, 100ml and 1000ml PVC bottles and on the 5mg/ml presentation in 20ml and 1000ml PVC bottles, under low humidity storage (40°C/25% and 25°C/40%) in accordance with the requirements for semi-permeable containers. No significant loss in water content was seen.

Only minor changes were seen in the test parameters following storage at 25°C/60% and 40°C/75%. An increase in loss on drying values was observed. Increase in density values was observed, possibly linked to the loss of water. The consequence of this is the need for a widening of the release limits. This does not indicate an unacceptable quality deficiency in the product.

The applicant has proposed a shelf-life of 3 years for product carrying the storage recommendations ‘Keep bottle in the outer carton’. No specific temperature
restrictions are proposed. The proposed shelf life is acceptable. The applicant has proposed an in-use shelf life for the multidose containers of 12 months. This is acceptable.

4.8.2 Post-approval stability protocol and stability commitment

A commitment has been provided that the ongoing studies on the production batches of the 1mg/ml presentation in each container will be continued to the end of the proposed studies.

A commitment has been provided that three manufacturing batches of each presentation of the 5mg/ml presentation will be initiated. Satisfactory protocol details have been provided.

4.9 BIOEQUIVALENCE/BIOAVAILABILITY

As the product is an oral solution, there is no need to demonstrate bioequivalence.

5. MAA FORM

The MAA forms are satisfactory.

6. SUMMARY OF PRODUCT CHARACTERISTICS (SPC)

The SPCs are satisfactory.

7. LABELLING

The labelling is satisfactory.

8. PATIENT INFORMATION LEAFLET

The leaflet mock-ups are satisfactory.

9. STATEMENT ABOUT THE AUTHOR OF THE OVERALL QUALITY SUMMARY

The Expert for the report on Quality is a suitably qualified person.

10. CONCLUSIONS

Marketing authorisations may be granted.
PRECLINICAL ASSESSMENT

No new preclinical data have been supplied with this application and none are required for an application of this type.
CLINICAL ASSESSMENT

1. INTRODUCTION

Methadone, the active ingredient in all these licence applications, is used either as an analgesic for moderate to severe pain or in the treatment of opioid drug addiction (as a narcotic abstinence syndrome suppressant).

2. BACKGROUND

Regulatory Pharma Net has applied for these licences as bibliographic applications.

3. INDICATIONS

These have already been outlined in the introduction. However, the final strength of the preparation to be dispensed to the patient must be specified on the prescription. (Many preparations are licensed for drug addiction only, though some have both indications)

4. DOSE & DOSE SCHEDULE

See MAA
A single dose of 5-10mg orally is the usual starting dose for the control of pain, repeated every 6-8 hours and adjusted to the degree of pain relief obtained.

For the control of addiction, 10-20mg are initially given per day, increasing by 10-20mg per day until there are no signs of withdrawal or intoxication, usually around 40-60mg/day.

5. TOXICOLOGY

No new data are presented and none are required for this application.

6. CLINICAL PHARMACOLOGY

No new data are presented and none are required for this application. There is a satisfactory overview of the pharmacodynamics and, in particular, the pharmacokinetics of methadone referring to papers published up to the year 2001. The pharmacokinetic interactions of methadone with antiretroviral drugs were particularly singled out since injection drug users infected with HIV are commonly opiate – dependent. Comment is also well made about the difficulty in devising a dosing schedule due to the marked interindividual variation in methadone pharmacokinetics.

7. EFFICACY
No new data are presented and none are required for this application. There is a satisfactory overview of clinical efficacy provided by the clinical expert. In it he refers to papers up to 2003, this last being a Cochrane review by Amato et al on the use of methadone at tapered doses. Other papers are reviewed back to the early 1980s.

8. SAFETY

No formal data are presented and none are required for this application. The clinical expert has provided a concise review of both clinical and non clinical toxicological studies and pharmacological class adverse events. His review includes papers between 1973 and 2001.

9. EXPERT REPORTS

There is a satisfactory clinical expert report from a suitably qualified person. His curriculum vitae is included.

10. SUMMARY OF PRODUCT CHARACTERISTICS (SPC)

The Summary of Product Characteristics is satisfactory.

11. PATIENT INFORMATION LEAFLET (PIL)

The Patient Information Leaflet is satisfactory.

12. LABELLING

The labelling is satisfactory

13. APPLICATION FORM (MAA)

The Marketing Authorisation Application is satisfactory.

14. DISCUSSION

These biographical applications for oral methadone hydrochloride have been satisfactorily supported by bibliographic references that have ranged back over 30 years, from 1973 to 2003.

15. RECOMMENDATION

Product licences may be granted.
OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY

The important quality characteristics of Eptadone Oral Solution are well defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

PRECLINICAL

No new preclinical data were submitted and none are required for applications of this type.

EFFICACY

Methadone hydrochloride is a well known drug and has been used as an opioid drug substitute and analgesic for many years.

No new or unexpected safety concerns arise from these applications.

The SPC, PIL and labelling are satisfactory.

RISK BENEFIT ASSESSMENT

The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. Extensive clinical experience with methadone hydrochloride is considered to have demonstrated the therapeutic value of the compound. The risk benefit is therefore considered to be positive.
## STEPS TAKEN FOR ASSESSMENT

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<thead>
<tr>
<th></th>
<th>Description</th>
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<tbody>
<tr>
<td>1</td>
<td>The MHRA received the marketing authorisation application on 13/05/2004.</td>
</tr>
<tr>
<td>2</td>
<td>Following standard checks and communication with the applicant the MHRA considered the application valid on 27/05/2004.</td>
</tr>
<tr>
<td>3</td>
<td>Following assessment of the application the MHRA requested further information relating to the clinical dossier on 14/01/2005.</td>
</tr>
<tr>
<td>4</td>
<td>The applicant responded to the MHRA’s requests, providing further information relating to the clinical dossier on 01/03/2005 and 23/05/2005.</td>
</tr>
<tr>
<td>5</td>
<td>Following assessment of the application the MHRA requested further information relating to the quality dossier on 05/04/2004 and 16/10/2005.</td>
</tr>
<tr>
<td>6</td>
<td>The applicant responded to the MHRA’s requests, providing further information on 28/06/2005 and 30/11/2005.</td>
</tr>
<tr>
<td>7</td>
<td>The application was determined on 13/04/2006.</td>
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EPTADONE ORAL SOLUTION (METHADONE HYDROCHLORIDE)
PL 20985/0001-6

STEPS TAKEN AFTER ASSESSMENT

<table>
<thead>
<tr>
<th>Date submitted</th>
<th>Application type</th>
<th>Scope</th>
<th>Outcome</th>
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</table>
SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

EPTADONE 1mg/ml oral solution

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each bottle contains 1mg/ml methadone hydrochloride in single dose bottles containing 20mg methadone hydrochloride

For excipients, see section 6.1

3. PHARMACEUTICAL FORM

Oral solution.

Clear liquid with lemon taste.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

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

For use as an analgesic for moderate to severe pain.

4.2. Posology and method of administration

For oral administration only.

<table>
<thead>
<tr>
<th>Addiction:</th>
<th>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</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADULTS.</td>
<td></td>
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</table>
dependence with the aim of gradual reduction.

<table>
<thead>
<tr>
<th>DEPENDENCY</th>
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<tr>
<td>ELDERLY.</td>
</tr>
<tr>
<td>CHILDREN.</td>
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</table>

**Pain:**

<table>
<thead>
<tr>
<th>ADULTS.</th>
</tr>
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<tbody>
<tr>
<td>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.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ELDERLY.</th>
</tr>
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<tbody>
<tr>
<td>Use caution with repeated dosage in elderly and ill patients.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CHILDREN.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not suitable.</td>
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</tbody>
</table>

4.3. **Contraindications**

Hypersensitivity to the active substance or to any of the excipients.
Respiratory depression, obstructive airways disease, concurrent administration with MAO inhibitors or within 2 weeks of discontinuation of treatment with them.
Patients dependent on non-opioid drugs.
Use during an asthma attack is not recommended.
Use during labour is not recommended, the prolonged duration of action increases the risk of neonatal depression.
Methadone is not suitable for children.

4.4. **Special warnings and precautions for use**

**Dependence.** Methadone is a drug of addiction and is controlled under the Misuse of Drugs Act 1971 (Schedule 2).
Methadone can cause a morphine-like drug dependence. Following repeated administrations, psychic dependence, physical dependence and tolerance can occur, therefore it must be prescribed and administered with the same caution utilized for morphine.
Extreme caution must be taken in the following cases:

- **Cranial lesions and high intracranial pressure.** The respiratory depressant effects of methadone and its capacity to increase the cerebrospinal fluid pressure can be considerably increased in the presence of an increase of the intracranial pressure; furthermore narcotics produce undesirable effects, that can hide neurological symptoms in patients with cranial lesions.
- **Asthma and other respiratory conditions.** In patients with acute asthma attacks, in those with chronic obstructive pulmonary disease or cor pulmonare and in individuals with a substantially decreased respiratory reserve in pre-existing respiratory depression, hypoxia or hypercapnia, even the usual therapeutic dosages...
of narcotics may reduce the respiratory drive and increase the airway resistance to the point of apnoea.

**Acute abdominal conditions.** The use of methadone or other narcotics may confound the diagnosis or the clinical course in patients with acute abdominal conditions.

**Hypotensive effect.** The administration of methadone can cause serious hypotension in hypovolemic subjects or with concomitant intake of medicinal products like phenothiazine or certain anaesthetics.

**Outpatient use.** In outpatients methadone may cause orthostatic hypotension.

**Use of narcotic antagonists.** In an individual with narcotic physical addiction, the administration of the usual dose of a narcotic antagonist can trigger an acute withdrawal syndrome. The severity of the syndrome will depend on the degree of physical dependence and on the dose of antagonist administered. The use of a narcotic antagonist in this subject should possibly be avoided. When this must be used for treatment of a severe respiratory depression in a patient physically addicted, the antagonist must be administered with extreme caution and gradually with dosages below the usual ones.

**Special risk patients.** Methadone must be administered with caution and the initial dose must be reduced in elderly and debilitated patients and patients with hypothyroidism, Addison’s disease, prostatic hypertrophy, urethral stricture. Caution should be exercised in patients with hepatic dysfunction or renal dysfunction.

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.

**Severe risk patients.** Suicide attempts with opiates, especially combined with tricyclic antidepressants, alcohol and other substances affecting the central nervous system, are part of the clinical features of dependency.

**Cardiac arrhythmia.** Since high doses of methadone have been associated with the occurrence of torsade de pointes (prolongation of the QT-interval), patients with risk factors for torsade de pointes should be treated with caution. The risk factors are:

- Electrolyte disorders, in particular hypokalaemia, hypocalcaemia and hypomagnesaemia.
- Congenital or acquired QT-prolongation.
- Cardiomyopathy, in particular in the presence of symptoms of cardiac failure.
- Sinus bradycardia.
- Symptomatic rhythm disorders.
- Concurrent medication known to prolong the QT-interval (in particular certain antiarrhythmics, neuroleptics, antibiotics, antidepressants and antihistaminics).

In patients for whom the potential benefits of a methadone-based treatment outweigh the risk of tachycardia onset, an electrocardiogram must be performed before therapy begins and after two weeks of treatment, with the aim of verifying and quantifying the effect of methadone hydrochloride on the QT interval. An electrocardiogram is also recommended before increasing the dose assumed.
Sucrose. Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

EPTADONE contains small amount of ethanol, less than 100mg per 100ml.

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

Pharmacokinetic interactions

Inhibitors of P-glycoprotein: methadone is a P-glycoprotein substrate, therefore all the drugs that inhibit it (quinidine, verapamil) can increase the serum concentration of methadone.

CYP3A4 isoenzyme inducers: the inducers of this isoenzyme (barbiturates, carbamazepine, phenytoin, nevirapine, rifampicin) can induce the hepatic metabolism, which could be more significant if the inducer is added after the methadone therapy has started. Following such interactions withdrawal symptom cases have been reported, therefore it was necessary to increase the dosage of methadone. When the CYP3A4 inducing drugs therapy is suspended, the dosage of methadone must be reduced.

CYP3A4 isoenzyme inhibitors: the interaction between methadone and cannabinoids (marijuana, hash, hemp, pot) has been proposed due to common CYP3A4 pathway. The interaction may result in altered or unpredictable metabolism. The interaction between clarithromycin and methadone as well as the interaction between erythromycin and methadone have been predicted due to the strong inhibition of CYP3A4 enzyme by erythromycin and clarithromycin. Clarithromycin and erythromycin may raise serum methadone level and/or increase methadone effects. The interaction between delavirdine and methadone has not been formally studied. It has been predicted due to the CYP3A4 inhibition by delavirdine, that may raise serum methadone level and/or increase methadone effects. Fluconazole has been shown to modify methadone kinetics in patients under methadone treatment. After 14 days of fluconazole 200 mg/day, serum methadone AUC and mean peak and trough concentrations increased by 35%, 27% and 48% respectively, while oral clearance was reduced by 24%. Although exposed to increased concentrations of methadone, patients exhibited neither signs of methadone overdose nor changes. The exact reason for this interaction is not fully understood, but a likely explanation is that fluconazole inhibits the metabolism of methadone because of its ability to inhibit several CYP enzymes, including CYP3A4 enzyme. The interaction between ketoconazole and methadone has been predicted due to CYP3A4 enzyme inhibition, that may raise serum methadone level and/or increase methadone effects. Because of extensive metabolism by the hepatic cytochrome P4503A4 system, itraconazole potentially interacts with drugs metabolized by this route. Itraconazole may decrease the elimination of drugs metabolized by CYP3A4 resulting in elevated plasma concentrations, which may prolong and/or increase both the therapeutic and the adverse effects of these drugs. Fluoxetine did not appear to alter the plasma methadone levels and no special precautions would therefore seem to be necessary if fluoxetine is added to
methadone. Paroxetine is a strong CYP2D6 inhibitor; at a dosage of 20 mg/day, significantly increased (R)-methadone concentrations in a group of eight CYP2D6 extensive metabolisers by a mean value of 32%.

Fluvoxamine has been shown to increase the plasma concentrations of both enantiomers of methadone. The reason appears to be that fluvoxamine can inhibit the liver metabolism of the methadone by cytochrome P450 isoenzyme CYP3A4, as confirmed by in vitro studies. The available information indicates that the effects of starting or stopping fluvoxamine should be monitored in patients on methadone, eventually adjusting the methadone dosage. Sertraline may inhibit methadone metabolism during the first few weeks of co-administration. Nefazodone is a potent inhibitor at CYP3A4 enzyme of the liver. No formal studies have been performed with co-administration of methadone and nefazodone, but an interaction has been predicted due to CYP3A4 enzyme inhibition, that may raise serum methadone level and/or increase methadone effects. Grapefruit Juice has a known inhibitory effect on CYP3A4 enzyme at intestinal level and P-glycoprotein. Juice administration is associated with a modest increase in methadone bioavailability, but it cannot be excluded that much stronger effect may occur in some patients, and thus grapefruit juice intake is not recommended during methadone treatment.

Didanosine and stavudine: methadone reduces the AUC and Cmax of didanosine and of stavudine, reducing the bioavailability of these drugs. Furthermore, methadone can slow down the absorption and increase the first passage metabolism of the aforementioned drugs.

Zidovudine: methadone increases the plasma concentration of zidovudine for both oral and intravenous administration, and also provokes an increase in the AUC of zidovudine for oral administration, more than for intravenous administration. Such effects are due to the inhibition of the glucuronidation of zidovudine and its reduced kidney clearance. During treatment with methadone, patients have to be monitored for a possible zidovudine toxicity, whereby it could be necessary to reduce the zidovudine dosage. The patients that take both drugs can develop typical symptoms of opioid withdrawal syndrome (headache, myalgia, fatigue and irritability).

Antiretroviral protease inhibitors: the antiretroviral protease inhibitors can inhibit the metabolism of methadone; the more significant reactions are obtained with ritonavir.

Abacavir: nineteen patients entering methadone treatment were given a single dose of abacavir (600 mg), begun methadone and, after 14 days, co-administered abacavir and methadone for the following 14 days. The results showed, in the last 14 days, a statistically significant increase (23%) in the rate of clearance of methadone, but no changes in the time to peak concentration or half-life. In addition, a significant decrease (34%) in the peak concentration and increase (67%) in the time to peak concentration of abacavir were observed in the first 14 days. The introduction of abacavir and amprenavir in 5 dependent patients in methadone treatment resulted in median decrease to 35% of the original concentration of methadone, with adverse effects compatible with withdrawal reactions in two patients.

Efavirenz: efavirenz induces the methadone metabolism through cytochrome P4503A4. Following a three-week therapy with efavirenz, the mean peak concentrations of methadone and the AUC were reduced by 48% and 57% respectively. Efavirenz added to a patient under methadone therapy...
could induce a withdrawal syndrome that usually starts after two weeks of efavirenz therapy, but can go on for up to 28 days. For this reason it may be necessary to adjust the methadone dosage.

**Nevirapine**: nevirapine induces methadone metabolism through cytochrome P450 family. The coadministration of nevirapine and methadone in twenty-five human immunodeficiency virus-infected subjects significantly decreased the mean dose-adjusted AUC of methadone by 41%. Methadone dose adjustments are justified when methadone is coadministered with nevirapine.

**Urine acidifiers**: methadone is a weak base. Urine acidifiers (ammonium chloride) can increase methadone kidney clearance. In this situation the methadone dosage should be increased.

**Pharmacodynamic interactions**

**Opioid agonists/antagonists**: naloxone and naltrexone antagonise the methadone action and provoke a withdrawal syndrome. Butorphanol, nalbuphine and pentazocine can partially block the analgesia and increase the respiratory and central nervous system (CNS) depression due to methadone. These drugs used in combination with methadone can provoke and increase neurological, respiratory and hypotensive effects. The additive or antagonist effects depend on the methadone dosage and are more frequent when the methadone dosage is low or moderate. These drugs can cause withdrawal syndrome in patients on chronic therapy.

**CNS depressant**: drugs with a depressive action on the CNS can provoke an increase of respiratory depression, therefore it may be necessary to decrease the dosage of one or both drugs.

**Antidiarrhoeals**: the concomitant use of methadone and antidiarrhoeals (diphenoxylate and loperamide) can cause severe constipation and an increased depression of the CNS. Opioid analgesics, combined with antimuscarinic drugs can cause severe constipation or paralytic ileus, especially with chronic use.

**Octreotide**: can reduce the analgesic effect of methadone and morphine, therefore if a reduction or loss of pain control occurs octreotide suspension has to be taken into consideration.

**Alcohol**: may induce serious respiratory depression and hypotension.

### 4.6. Pregnancy and lactation

**Pregnancy**

There is no, or inadequate evidence of safety in human pregnancy. Female addicts who are pregnant will require specialised care from obstetric and paediatric staff with experience in such management. A careful risk benefit assessment should be made before administration to pregnant women. Possible adverse effects on the foetus and neonate include respiratory depression, low birth weight, neonatal withdrawal syndrome and increased rate of stillbirths. During labour there is a risk of gastric stasis and inhalation pneumonia in the mother.
4.7. Effects on ability to drive and use machines

Patients should not drive or use machines while taking methadone. Methadone may cause drowsiness and reduce alertness and the ability to drive. 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

Respiratory Systems: From very common (≥ 1/10) to common (≥ 1/100, < 1/10): respiratory depression. From uncommon (≥ 1/100, < 1/1000) to rare (≥ 1/10000, < 1/1000): respiratory arrest.

Central nervous system: From very common (≥ 1/10) to common (≥ 1/100, < 1/10): euphoria, dysphoria, weakness, headache, sedation, insomnia, agitation, disorientation, feeling of empty head, visual disturbances, dizziness, miosis.

Gastrointestinal tract and liver: From very common (≥ 1/10) to common (≥ 1/100, < 1/10): nausea, vomiting, constipation, xerostomia, anorexia and spasms of the biliary tract.

Cardiovascular apparatus: From very common (≥ 1/10) to common (≥ 1/100, < 1/10): rushing, bradycardia, palpitations, fainting, orthostatic hypotension and syncope. From uncommon (≥ 1/100, < 1/1000) to rare (≥ 1/10000, < 1/1000): shock and cardiac arrest. Torsade de pointes can also occur with high doses.

Urinary-genital apparatus: From very common (≥ 1/10) to common (≥ 1/100, < 1/10): urinary retention and difficulty to urinate, anti-diuretic effect and libido reduction and/or sexual impotence.

Skin and Annexes: From very common (≥ 1/10) to common (≥ 1/100, < 1/10): excessive sweating, itchiness, nettle rash, other skin reactions, oedema. From uncommon (≥ 1/100, < 1/1000) to rare (≥ 1/10000, < 1/1000): hemorrhagic nettle rash.

Blood: From uncommon (≥ 1/100, < 1/1000) to rare (≥ 1/10000, < 1/1000): haemorrhagia

Endocrine Systems: From uncommon (≥ 1/100, < 1/1000) to rare (≥ 1/10000, < 1/1000): Long-term administration may produce raised prolactin levels.

Possible undesirable effects due to excipients: the medicinal product contains the following excipient that may cause undesirable effects: glycerol (harmful at high doses): may cause headache, stomach upset and diarrhoea.

Lactation
Methadone is excreted in breast milk and may cause respiratory depression in the newborn. Breast feeding is usually not recommended. However, a careful risk benefit assessment case by case is suggested, taking into account that methadone could prevent the possibility of an overdose syndrome in the newborn.
4.9. Overdose

Symptoms and signs: similar to those for morphine. 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.

Treatment: treatment is supportive. Patients should be kept conscious wherever possible. 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 Levallophan (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

Pharmacotherapeutic group: drugs used in opioid dependence
ATC code: N07BC02

Methadone is a strong opioid agonist with actions predominantly at the μ receptor. The analgesic activity of the racemate is almost entirely due to the l-isomer, which is at least 10 times more potent as an analgesic than the d-isomer. The d-isomer lacks significant respiratory depressant activity but does have anti-tussive effects. Methadone also has some agonist actions at the K and δ opiate receptors. These actions result in analgesia, depression of respiration, suppression of cough, nausea and vomiting (via an effect on the chemoceptor 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
Methadone is a basic and lipophilic drug, which is rapidly absorbed from the gastrointestinal tract with peak plasma levels between 1.5 and 3 h and an oral bioavailability of no less than 80%. Its pharmacokinetics are characterized by a rapid and extensive distribution phase followed by a slow elimination phase. The drug is subjected to considerable tissue distribution, yielding a relatively high volume of distribution and it is largely bound to plasma proteins (approximately 89%). The sequestration of methadone at extravascular binding sites, followed by slow release into plasma, contributes to the prolonged duration of methadone half-life in plasma and urine. Pharmacokinetic studies in normal individuals, postoperative patients and methadone maintenance patients indicate that methadone has a variable (both within and among studies) terminal elimination half-life, with mean values ranging from 19 to 55 hours. Thus, there is potential for accumulation when methadone is administered at short intervals. The relative unpredictability of methadone pharmacokinetics renders difficult to devise a uniform dosing schedule and underlines the importance of individualized dosage. The oxidative biotransformation of methadone is the main route of drug elimination, which occurs primarily in the liver. In the first 96 h after administration, 15-60% can be recovered from the urine. The two major urinary metabolite lack pharmacological activity. Urinary pH is an important determinant of elimination half-life.

5.3. Preclinical safety data

Not applicable.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

- Sucrose
- Glycerol
- Sodium Benzoate (E211)
- Citric Acid monohydrate
- Lemon Flavour (including Citropten, Citral, and ethanol)
- Purified Water.

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

3 years.
6.4. **Special precautions for storage**

Keep bottle in the outer carton.

6.5. **Nature and contents of container**

Amber, transparent, non-plasticised PVC 25-ml bottle with aluminium pilfer proof screw cap fitted with polyethylene liner, equipped with a cover-cap to make it child resistant.

6.6. **Instruction for use and handling**

No special requirements.

7. **MARKETING AUTHORISATION HOLDER**

Regulatory Pharma Net s.r.l.
Corso Italia, 108
I-56125 PISA
Italy

8. **MARKETING AUTHORISATION NUMBER**

PL 20985/0001

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

13/04/2006

10. **DATE OF REVISION OF THE TEXT**

13/04/2006
1. NAME OF THE MEDICINAL PRODUCT

EPTADONE 1mg/ml oral solution.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each bottle contains 1mg/ml methadone hydrochloride in single dose bottles containing 40mg methadone hydrochloride

For excipients, see section 6.1

3. PHARMACEUTICAL FORM

Oral solution.

Clear liquid with lemon taste.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

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

For use as an analgesic for moderate to severe pain.

4.2. Posology and method of administration

For oral administration only.

<table>
<thead>
<tr>
<th>Addiction:</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>ADULTS.</td>
<td>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.</td>
</tr>
</tbody>
</table>

For oral administration only.
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.

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### 4.3. Contraindications

Hypersensitivity to the active substance or to any of the excipients.
Respiratory depression, obstructive airways disease, concurrent administration with MAO inhibitors or within 2 weeks of discontinuation of treatment with them.
Patients dependent on non-opioid drugs.
Use during an asthma attack is not recommended.
Use during labour is not recommended, the prolonged duration of action increases the risk of neonatal depression.
Methadone is not suitable for children.

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### 4.4. Special warnings and precautions for use

**Dependence.** Methadone is a drug of addiction and is controlled under the Misuse of Drugs Act 1971 (Schedule 2).
Methadone can cause a morphine-like drug dependence. Following repeated administrations, psychic dependence, physical dependence and tolerance can occur, therefore it must be prescribed and administered with the same caution utilized for morphine.
Extreme caution must be taken in the following cases:

**Cranial lesions and high intracranial pressure.** The respiratory depressant effects of methadone and its capacity to increase the cerebrospinal fluid pressure can be considerably increased in the presence of an increase of the intracranial pressure; furthermore narcotics produce undesirable effects, that can hide neurological symptoms in patients with cranial lesions.

**Asthma and other respiratory conditions.** In patients with acute asthma attacks, in those with chronic obstructive pulmonary disease or cor pulmonare and in individuals with a substantially decreased respiratory reserve in pre-existing respiratory depression, hypoxia or hypercapnia, even the usual therapeutic dosages of narcotics may reduce the respiratory drive and increase the airway resistance to the point of apnoea.
Acute abdominal conditions. The use of methadone or other narcotics may confound the diagnosis or the clinical course in patients with acute abdominal conditions.

Hypotensive effect. The administration of methadone can cause serious hypotension in hypovolemic subjects or with concomitant intake of medicinal products like phenothiazine or certain anaesthetics.

Outpatient use. In outpatients methadone may cause orthostatic hypotension.

Use of narcotic antagonists. In an individual with narcotic physical addiction, the administration of the usual dose of a narcotic antagonist can trigger an acute withdrawal syndrome. The severity of the syndrome will depend on the degree of physical dependence and on the dose of antagonist administered. The use of a narcotic antagonist in this subject should possibly be avoided. When this must be used for treatment of a severe respiratory depression in a patient physically addicted, the antagonist must be administered with extreme caution and gradually with dosages below the usual ones.

Special risk patients. Methadone must be administered with caution and the initial dose must be reduced in elderly and debilitated patients and patients with hypothyroidism, Addison’s disease, prostatic hypertrophy, urethral stricture.

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

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.

Severe risk patients. Suicide attempts with opiates, especially combined with tricyclic antidepressants, alcohol and other substances affecting the central nervous system, are part of the clinical features of dependency.

Cardiac arrhythmia. Since high doses of methadone have been associated with the occurrence of torsade de pointes (prolongation of the QT-interval), patients with risk factors for torsade de pointes should be treated with caution. The risk factors are:

- Electrolyte disorders, in particular hypokalaemia, hypocalcaemia and hypomagnesaemia.
- Congenital or acquired QT-prolongation.
- Cardiomyopathy, in particular in the presence of symptoms of cardiac failure.
- Sinus bradycardia.
- Symptomatic rhythm disorders.
- Concurrent medication known to prolong the QT-interval (in particular certain antiarrhythmics, neuroleptics, antibiotics, antidepressants and antihistaminics).

In patients for whom the potential benefits of a methadone-based treatment outweigh the risk of tachycardia onset, an electrocardiogram must be performed before therapy begins and after two weeks of treatment, with the aim of verifying and quantifying the effect of methadone hydrochloride on the QT interval. An electrocardiogram is also recommended before increasing the dose assumed.
Sucrose. Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

EPTADONE contains small amount of ethanol, less than 100mg per 100ml.

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CYP3A4 isoenzyme inducers: the inducers of this isoenzyme (barbiturates, carbamazepine, phenytoin, nevirapine, rifampicin) can induce the hepatic metabolism, which could be more significant if the inducer is added after the methadone therapy has started. Following such interactions withdrawal symptom cases have been reported, therefore it was necessary to increase the dosage of methadone. When the CYP3A4 inducing drugs therapy is suspended, the dosage of methadone must be reduced.

CYP3A4 isoenzyme inhibitors: the interaction between methadone and cannabinoids (marijuana, hash, hemp, pot) has been proposed due to common CYP3A4 pathway. The interaction may result in altered or unpredictable metabolism. The interaction between clarithromycin and methadone as well as the interaction between erithromycin and methadone have been predicted due to the strong inhibition of CYP3A4 enzyme by erithromycin and clarithromycin. Clarithromycin and erithromycin may raise serum methadone level and/or increase methadone effects. The interaction between delavirdine and methadone has not been formally studied. It has been predicted due to the CYP3A4 inhibition by delavirdine, that may raise serum methadone level and/or increase methadone effects. Fluconazole has been shown to modify methadone kinetics in patients under methadone treatment. After 14 days of fluconazole 200 mg/day, serum methadone AUC and mean peak and trough concentrations increased by 35%, 27% and 48% respectively, while oral clearance was reduced by 24 %. Although exposed to increased concentrations of methadone, patients exhibited neither signs of methadone overdose nor changes. The exact reason for this interaction is not fully understood, but a likely explanation is that fluconazole inhibits the metabolism of methadone because of its ability to inhibit several CYP enzymes, including CYP3A4 enzyme. The interaction between ketoconazole and methadone has been predicted due to CYP3A4 enzyme inhibition, that may raise serum methadone level and/or increase methadone effects. Because of extensive metabolism by the hepatic cytochrome P4503A4 system, itraconazole potentially interacts with drugs metabolized by this route. Itraconazole may decrease the elimination of drugs metabolized by CYP3A4 resulting in elevated plasma concentrations, which may prolong and/or increase both the therapeutic and the adverse effects of these drugs. Fluoxetine did not appear to alter the plasma methadone levels and no special precautions would therefore seem to be necessary if fluoxetine is added to methadone. Paroxetine is a strong CYP2D6 inhibitor; at a
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Antidiarrhoeals: the concomitant use of methadone and antidiarrhoeals (diphenoxylate and loperamide) can cause severe constipation and an increased depression of the CNS. Opioid analgesics, combined with antimuscarinic drugs can cause severe constipation or paralytic ileus, especially with chronic use.

Octreotide: can reduce the analgesic effect of methadone and morphine, therefore if a reduction or loss of pain control occurs octreotide suspension has to be taken into consideration.

Alcohol: may induce serious respiratory depression and hypotension.

### 4.6. Pregnancy and lactation

**Pregnancy**

There is no, or inadequate evidence of safety in human pregnancy. Female addicts who are pregnant will require specialised care from obstetric and paediatric staff with experience in such management. A careful risk benefit assessment should be made before administration to pregnant women. Possible adverse effects on the foetus and neonate include respiratory depression, low birth weight, neonatal withdrawal syndrome and increased rate of stillbirths. During labour there is a risk of gastric stasis and inhalation pneumonia in the mother.
Lactation
Methadone is excreted in breast milk and may cause respiratory depression in the newborn. Breast feeding is usually not recommended. However, a careful risk benefit assessment case by case is suggested, taking into account that methadone could prevent the possibility of an overdose syndrome in the newborn.

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Patients should not drive or use machines while taking methadone. Methadone may cause drowsiness and reduce alertness and the ability to drive. The time after which such activities may be safely resumed is extremely patient-dependent and must be decided by the Physician.

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Respiratory Systems: From very common (≥ 1/10) to common (≥ 1/100, < 1/10): respiratory depression.
From uncommon (≥ 1/100, < 1/1000) to rare (≥ 1/100000, < 1/1000): respiratory arrest.

Central nervous system: From very common (≥ 1/10) to common (≥ 1/100, < 1/10): euphoria, dysphoria, weakness, headache, sedation, insomnia, agitation, disorientation, feeling of empty head, visual disturbances, dizziness, miosis.

Gastrointestinal tract and liver: From very common (≥ 1/10) to common (≥ 1/100, < 1/10): nausea, vomiting, constipation, xerostomia, anorexia and spasms of the biliary tract.
Cardiovascular apparatus: From very common (≥ 1/10) to common (≥ 1/100, < 1/10): rushing, bradycardia, palpitations, fainting, orthostatic hypotension and syncope.
From uncommon (≥ 1/100, < 1/1000) to rare (≥ 1/100000, < 1/1000): shock and cardiac arrest. Torsade de pointes can also occur with high doses.

Urinary-genital apparatus: From very common (≥ 1/10) to common (≥ 1/100, < 1/10): urinary retention and difficulty to urinate, anti-diuretic effect and libido reduction and/or sexual impotence.
Skin and Annexes: From very common (≥ 1/10) to common (≥ 1/100, < 1/10): excessive sweating, itchiness, nettle rash, other skin reactions, oedema. From uncommon (≥ 1/100, < 1/1000) to rare (≥ 1/100000, < 1/1000): hemorrhagic nettle rash.
Blood: From uncommon (≥ 1/100, < 1/1000) to rare (≥ 1/100000, < 1/1000): haemorrhagia
Endocrine Systems: From uncommon (≥ 1/100, < 1/1000) to rare (≥ 1/100000, < 1/1000): Long-term administration may produce raised prolactin levels.

Possible undesirable effects due to excipients: the medicinal product contains the following excipient that may cause undesirable effects: glycerol (harmful at high
doses): may cause headache, stomach upset and diarrhoea.

4.9. **Overdose**

**Symptoms and signs:** similar to those for morphine. 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.

**Treatment:** treatment is supportive. Patients should be kept conscious wherever possible. 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.

5. **PHARMACOLOGICAL PROPERTIES**

5.1. **Pharmacodynamic properties**

Pharmacotherapeutic group: drugs used in opioid dependence
ATC code: N07BC02

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

Methadone is a basic and lipophilic drug, which is rapidly absorbed from the gastrointestinal tract with peak plasma levels between 1.5 and 3 h and an oral bioavailability of no less than 80%. Its pharmacokinetics are characterized by a rapid and extensive distribution phase followed by a slow elimination phase. The drug is subjected to considerable tissue distribution, yielding a relatively high volume of distribution and it is largely bound to plasma proteins (approximately 89%). The sequestration of methadone at extravascular binding sites, followed by slow release into plasma, contributes to the prolonged duration of methadone half-life in plasma and urine. Pharmacokinetic studies in normal individuals, postoperative patients and methadone maintenance patients indicate that methadone has a variable (both within and among studies) terminal elimination half-life, with mean values ranging from 19 to 55 hours. Thus, there is potential for accumulation when methadone is administered at short intervals. The relative unpredictability of methadone pharmacokinetics renders difficult to devise a uniform dosing schedule and underlines the importance of individualized dosage. The oxidative biotransformation of methadone is the main route of drug elimination, which occurs primarily in the liver. In the first 96 h after administration, 15-60% can be recovered from the urine. The two major urinary metabolite lack pharmacological activity. Urinary pH is an important determinant of elimination half-life.

5.3. **Preclinical safety data**

Not applicable.

6. **PHARMACEUTICAL PARTICULARS**

6.1. **List of excipients**

- Sucrose
- Glycerol
- Sodium Benzoate (E211)
- Citric Acid monohydrate
- Lemon Flavour (including Citropten, Citral, and ethanol)
- Purified Water.

6.2. **Incompatibilities**

Not applicable.

6.3. **Shelf life**

3 years.
6.4. Special precautions for storage

Keep bottle in the outer carton.

6.5. Nature and contents of container

Amber, transparent, non-plasticised PVC 60-ml bottle with aluminium pilfer proof screw cap fitted with polyethylene liner, equipped with a cover-cap to make it child resistant.

6.6. Instruction for use and handling

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Regulatory Pharma Net s.r.l.
Corso Italia, 108
I-56125 PISA
Italy

8. MARKETING AUTHORISATION NUMBER

PL 20985/0002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

13/04/2006

10. DATE OF REVISION OF THE TEXT
1. **NAME OF THE MEDICINAL PRODUCT**

   EPTADONE 1mg/ml oral solution.

2. **QUALITATIVE AND QUANTITATIVE COMPOSITION**

   Each bottle contains 1mg/ml methadone hydrochloride in single dose bottles containing 60mg methadone hydrochloride

   For excipients, see section 6.1

3. **PHARMACEUTICAL FORM**

   Oral solution.

   Clear liquid with lemon taste.

4. **CLINICAL PARTICULARS**

4.1. **Therapeutic indications**

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

   For use as an analgesic for moderate to severe pain.

4.2. **Posology and method of administration**

   For oral administration only.

<table>
<thead>
<tr>
<th>Addiction:</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ADULTS.</strong></td>
</tr>
<tr>
<td>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.</td>
</tr>
<tr>
<td><strong>ELDERLY.</strong></td>
</tr>
<tr>
<td>In the case of the elderly or ill patients repeated doses should only be given with extreme caution.</td>
</tr>
<tr>
<td>CHILDREN.</td>
</tr>
<tr>
<td>---</td>
</tr>
<tr>
<td>Pain:</td>
</tr>
<tr>
<td>ADULTS.</td>
</tr>
<tr>
<td>ELDERLY.</td>
</tr>
<tr>
<td>CHILDREN.</td>
</tr>
</tbody>
</table>

4.3. **Contraindications**

Hypersensitivity to the active substance or to any of the excipients. 
Respiratory depression, obstructive airways disease, concurrent administration with MAO inhibitors or within 2 weeks of discontinuation of treatment with them. 
Patients dependent on non-opioid drugs. 
Use during an asthma attack is not recommended. 
Use during labour is not recommended, the prolonged duration of action increases the risk of neonatal depression. 
Methadone is not suitable for children.

4.4. **Special warnings and precautions for use**

**Dependence.** Methadone is a drug of addiction and is controlled under the Misuse of Drugs Act 1971 (Schedule 2). Methadone can cause a morphine-like drug dependence. Following repeated administrations, psychic dependence, physical dependence and tolerance can occur, therefore it must be prescribed and administered with the same caution utilized for morphine. 
Extreme caution must be taken in the following cases: 
**Cranial lesions and high intracranial pressure.** The respiratory depressant effects of methadone and its capacity to increase the cerebrospinal fluid pressure can be considerably increased in the presence of an increase of the intracranial pressure; furthermore narcotics produce undesirable effects, that can hide neurological symptoms in patients with cranial lesions. 
**Asthma and other respiratory conditions.** In patients with acute asthma attacks, in those with chronic obstructive pulmonary disease or cor pulmonare and in individuals with a substantially decreased respiratory reserve in pre-existing respiratory depression, hypoxia or hypercapnia, even the usual therapeutic dosages of narcotics may reduce the respiratory drive and increase the airway resistance to the point of apnoea. 
**Acute abdominal conditions.** The use of methadone or other narcotics may confound the diagnosis or the clinical course in patients with acute abdominal conditions.
Hypotensive effect. The administration of methadone can cause serious hypotension in hypovolemic subjects or with concomitant intake of medicinal products like phenothiazine or certain anaesthetics.

Outpatient use. In outpatients methadone may cause orthostatic hypotension.

Use of narcotic antagonists. In an individual with narcotic physical addiction, the administration of the usual dose of a narcotic antagonist can trigger an acute withdrawal syndrome. The severity of the syndrome will depend on the degree of physical dependence and on the dose of antagonist administered. The use of a narcotic antagonist in this subject should possibly be avoided. When this must be used for treatment of a severe respiratory depression in a patient physically addicted, the antagonist must be administered with extreme caution and gradually with dosages below the usual ones.

Special risk patients. Methadone must be administered with caution and the initial dose must be reduced in elderly and debilitated patients and patients with hypothyroidism, Addison’s disease, prostatic hypertrophy, urethral stricture.

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

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.

Severe risk patients. Suicide attempts with opiates, especially combined with tricyclic antidepressants, alcohol and other substances affecting the central nervous system, are part of the clinical features of dependency.

Cardiac arrhythmia. Since high doses of methadone have been associated with the occurrence of torsade de pointes (prolongation of the QT-interval), patients with risk factors for torsade de pointes should be treated with caution. The risk factors are:

- Electrolyte disorders, in particular hypokalaemia, hypocalcaemia and hypomagnesaemia.
- Congenital or acquired QT-prolongation.
- Cardiomyopathy, in particular in the presence of symptoms of cardiac failure.
- Sinus bradycardia.
- Symptomatic rhythm disorders.
- Concurrent medication known to prolong the QT-interval (in particular certain antiarrhythmics, neuroleptics, antibiotics, antidepressants and antihistaminics).

In patients for whom the potential benefits of a methadone-based treatment outweigh the risk of tachycardia onset, an electrocardiogram must be performed before therapy begins and after two weeks of treatment, with the aim of verifying and quantifying the effect of methadone hydrochloride on the QT interval. An electrocardiogram is also recommended before increasing the dose assumed.

Sucrose. Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

EPTADONE contains small amount of ethanol, less than 100mg per 100ml.
4.5. Interactions with other medicinal products and other forms of interaction

**Pharmacokinetic interactions**

Inhibitors of P-glycoprotein: methadone is a P-glycoprotein substrate, therefore all the drugs that inhibit it (quinidine, verapamil) can increase the serum concentration of methadone.

**CYP3A4 isoenzyme inducers:** the inducers of this isoenzyme (barbiturates, carbamazepine, phenytoin, nevirapine, rifampicin) can induce the hepatic metabolism, which could be more significant if the inducer is added after the methadone therapy has started. Following such interactions withdrawal symptom cases have been reported, therefore it was necessary to increase the dosage of methadone. When the CYP3A4 inducing drugs therapy is suspended, the dosage of methadone must be reduced.

**CYP3A4 isoenzyme inhibitors:** the interaction between methadone and cannabinoids (marijuana, hash, hemp, pot) has been proposed due to common CYP3A4 pathway. The interaction may result in altered or unpredictable metabolism. The interaction between clarithromycin and methadone as well as the interaction between erithromycin and methadone have been predicted due to the strong inhibition of CYP3A4 enzyme by erithomycin and clarithromycin. Clarithromycin and erithromycin may raise serum methadone level and/or increase methadone effects. The interaction between delavirdine and methadone has not been formally studied. It has been predicted due to the CYP3A4 inhibition by delavirdine, that may raise serum methadone level and/or increase methadone effects. Fluconazole has been shown to modify methadone kinetics in patients under methadone treatment. After 14 days of fluconazole 200 mg/day, serum methadone AUC and mean peak and trough concentrations increased by 35%, 27% and 48% respectively, while oral clearance was reduced by 24%. Although exposed to increased concentrations of methadone, patients exhibited neither signs of methadone overdose nor changes. The exact reason for this interaction is not fully understood, but a likely explanation is that fluconazole inhibits the metabolism of methadone because of its ability to inhibit several CYP enzymes, including CYP3A4 enzyme. The interaction between ketoconazole and methadone has been predicted due to CYP3A4 enzyme inhibition, that may raise serum methadone level and/or increase methadone effects. Ketoconazole may decrease the elimination of drugs metabolized by CYP3A4 resulting in elevated plasma concentrations, which may prolong and/or increase both the therapeutic and the adverse effects of these drugs. Fluoxetine did not appear to alter the plasma methadone levels and no special precautions would therefore seem to be necessary if fluoxetine is added to methadone. Paroxetine is a strong CYP2D6 inhibitor; at a dosage of 20 mg/day, significantly increased (R)-methadone concentrations in a group of eight CYP2D6 extensive metabolisers by a mean value of 32%.

Fluvoxamine has been shown to increase the plasma concentrations of both enantiomers of methadone. The reason appears to be that fluvoxamine can inhibit the liver metabolism of the methadone by cytochrome P450 isoenzyme CYP3A4, as
confirmed by *in vitro* studies. The available information indicates that the effects of starting or stopping fluvoxamine should be monitored in patients on methadone, eventually adjusting the methadone dosage. Sertraline may inhibit methadone metabolism during the first few weeks of co-administration. Nefazodone is a potent inhibitor at CYP3A4 enzyme of the liver. No formal studies have been performed with co-administration of methadone and nefazodone, but an interaction has been predicted due to CYP3A4 enzyme inhibition, that may raise serum methadone level and/or increase methadone effects. Grapefruit Juice has a known inhibitory effect on CYP3A4 enzyme at intestinal level and P-glycoprotein. Juice administration is associated with a modest increase in methadone bioavailability, but it cannot be excluded that much stronger effect may occur in some patients, and thus grapefruit juice intake is not recommended during methadone treatment.

*Didanosine and stavudine*: methadone reduces the AUC and Cmax of didanosine and of stavudine, reducing the bioavailability of these drugs. Furthermore, methadone can slow down the absorption and increase the first passage metabolism of the aforementioned drugs.

*Zidovudine*: methadone increases the plasma concentration of zidovudine for both oral and intravenous administration, and also provokes an increase in the AUC of zidovudine for oral administration, more than for intravenous administration. Such effects are due to the inhibition of the glucuronidation of zidovudine and its reduced kidney clearance. During treatment with methadone, patients have to be monitored for a possible zidovudine toxicity, whereby it could be necessary to reduce the zidovudine dosage. The patients that take both drugs can develop typical symptoms of opioid withdrawal syndrome (headache, myalgia, fatigue and irritability).

*Antiretroviral protease inhibitors*: the antiretroviral protease inhibitors can inhibit the metabolism of methadone; the more significant reactions are obtained with ritonavir.

*Abacavir*: nineteen patients entering methadone treatment were given a single dose of abacavir (600 mg), begun methadone and, after 14 days, co-administered abacavir and methadone for the following 14 days. The results showed, in the last 14 days, a statistically significant increase (23%) in the rate of clearance of methadone, but no changes in the time to peak concentration or half-life. In addition, a significant decrease (34%) in the peak concentration and increase (67%) in the time to peak concentration of abacavir were observed in the first 14 days. The introduction of abacavir and amprenavir in 5 dependent patients in methadone treatment resulted in median decrease to 35% of the original concentration of methadone, with adverse effects compatible with withdrawal reactions in two patients.

*Efavirenz*: efavirenz induces the methadone metabolism through cytochrome P4503A4. Following a three-week therapy with efavirenz, the mean peak concentrations of methadone and the AUC were reduced by 48% and 57% respectively. Efavirenz added to a patient under methadone therapy could induce a withdrawal syndrome that usually starts after two weeks of efavirenz therapy, but can go on for up to 28 days. For this reason it may be necessary to adjust the methadone dosage.

*Nevirapine*: nevirapine induces methadone metabolism through cytochrome P450 family. The coadministration of nevirapine and methadone in twenty-five human immunodeficiency virus-infected subjects significantly decreased the mean dose-
adjusted AUC of methadone by 41%. Methadone dose adjustments are justified when methadone is coadministered with nevirapine. **Urine acidifiers:** methadone is a weak base. Urine acidifiers (ammonium chloride) can increase methadone kidney clearance. In this situation the methadone dosage should be increased.

**Pharmacodynamic interactions**

**Opioid agonists/antagonists:** naloxone and naltrexone antagonise the methadone action and provoke a withdrawal syndrome. Butorphanol, nalbuphine and pentazocine can partially block the analgesia and increase the respiratory and central nervous system (CNS) depression due to methadone. These drugs used in combination with methadone can provoke and increase neurological, respiratory and hypotensive effects. The additive or antagonist effects depend on the methadone dosage and are more frequent when the methadone dosage is low or moderate. These drugs can cause withdrawal syndrome in patients on chronic therapy. **CNS depressant:** drugs with a depressive action on the CNS can provoke an increase of respiratory depression, therefore it may be necessary to decrease the dosage of one or both drugs. **Antidiarrhoeals:** the concomitant use of methadone and antidiarrhoeals (diphenoxylate and loperamide) can cause severe constipation and an increased depression of the CNS. Opioid analgesics, combined with antimuscarinic drugs can cause severe constipation or paralytic ileus, especially with chronic use. **Octreotide:** can reduce the analgesic effect of methadone and morphine, therefore if a reduction or loss of pain control occurs octreotide suspension has to be taken into consideration. **Alcohol:** may induce serious respiratory depression and hypotension.

### 4.6. Pregnancy and lactation

**Pregnancy**

There is no, or inadequate evidence of safety in human pregnancy. Female addicts who are pregnant will require specialised care from obstetric and paediatric staff with experience in such management. A careful risk benefit assessment should be made before administration to pregnant women. Possible adverse effects on the foetus and neonate include respiratory depression, low birth weight, neonatal withdrawal syndrome and increased rate of stillbirths. During labour there is a risk of gastric stasis and inhalation pneumonia in the mother.

**Lactation**

Methadone is excreted in breast milk and may cause respiratory depression in the newborn. Breast feeding is usually not recommended. However, a careful risk benefit assessment case by case is suggested, taking into account that methadone could prevent the possibility of an overdose syndrome in the newborn.
4.7. **Effects on ability to drive and use machines**

Patients should not drive or use machines while taking methadone. Methadone may cause drowsiness and reduce alertness and the ability to drive. 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**

**Respiratory Systems**: From very common (≥ 1/10) to common (≥ 1/100, < 1/10): respiratory depression. From uncommon (≥ 1/100, < 1/1000) to rare (≥ 1/10000, < 1/1000): respiratory arrest.

**Central nervous system**: From very common (≥ 1/10) to common (≥ 1/100, < 1/10): euphoria, dysphoria, weakness, headache, sedation, insomnia, agitation, disorientation, feeling of empty head, visual disturbances, dizziness, miosis.

**Gastrointestinal tract and liver**: From very common (≥ 1/10) to common (≥ 1/100, < 1/10): nausea, vomiting, constipation, xerostomia, anorexia and spasms of the biliary tract.

**Cardiovascular apparatus**: From very common (≥ 1/10) to common (≥ 1/100, < 1/10): rushing, bradycardia, palpitations, fainting, orthostatic hypotension and syncope. From uncommon (≥ 1/100, < 1/1000) to rare (≥ 1/10000, < 1/1000): shock and cardiac arrest. Torsade de pointes can also occur with high doses.

**Urinary-genital apparatus**: From very common (≥ 1/10) to common (≥ 1/100, < 1/10): urinary retention and difficulty to urinate, anti-diuretic effect and libido reduction and/or sexual impotence.

**Skin and Annexes**: From very common (≥ 1/10) to common (≥ 1/100, < 1/10): excessive sweating, itchiness, nettle rash, other skin reactions, oedema. From uncommon (≥ 1/100, < 1/1000) to rare (≥ 1/10000, < 1/1000): hemorrhagic nettle rash.

**Blood**: From uncommon (≥ 1/100, < 1/1000) to rare (≥ 1/10000, < 1/1000): haemorrhagia

**Endocrine Systems**: From uncommon (≥ 1/100, < 1/1000) to rare (≥ 1/10000, < 1/1000): Long-term administration may produce raised prolactin levels.

**Possible undesirable effects due to excipients**: the medicinal product contains the following excipient that may cause undesirable effects: glycerol (harmful at high doses): may cause headache, stomach upset and diarrhoea.

4.9. **Overdose**

**Symptoms and signs**: similar to those for morphine. 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.

**Treatment**: treatment is supportive. Patients should be kept conscious wherever possible. 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.

5. **PHARMACOLOGICAL PROPERTIES**

5.1. **Pharmacodynamic properties**

Pharmacotherapeutic group: drugs used in opioid dependence  
ATC code: N07BC02  
Methadone is a strong opioid agonist with actions predominantly at the µ receptor. The analgesic activity of the racemate is almost entirely due to the l-isomer, which is at least 10 times more potent as an analgesic than the d-isomer. The d-isomer lacks significant respiratory depressant activity but does have anti-tussive effects. Methadone also has some agonist actions at the 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**

Methadone is a basic and lipophilic drug, which is rapidly absorbed from the gastrointestinal tract with peak plasma levels between 1.5 and 3 h and an oral bioavailability of no less than 80%. Its pharmacokinetics are characterized by a rapid and extensive distribution phase followed by a slow elimination phase. The drug is subjected to considerable tissue distribution, yielding a relatively high...
volume of distribution and it is largely bound to plasma proteins (approximately 89%). The sequestration of methadone at extravascular binding sites, followed by slow release into plasma, contributes to the prolonged duration of methadone half-life in plasma and urine. Pharmacokinetic studies in normal individuals, postoperative patients and methadone maintenance patients indicate that methadone has a variable (both within and among studies) terminal elimination half-life, with mean values ranging from 19 to 55 hours. Thus, there is potential for accumulation when methadone is administered at short intervals. The relative unpredictability of methadone pharmacokinetics renders difficult to devise a uniform dosing schedule and underlines the importance of individualized dosage. The oxidative biotransformation of methadone is the main route of drug elimination, which occurs primarily in the liver. In the first 96 h after administration, 15-60% can be recovered from the urine. The two major urinary metabolite lack pharmacological activity. Urinary pH is an important determinant of elimination half-life.

5.3. Preclinical safety data

Not applicable.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Sucrose
Glycerol
Sodium Benzoate (E211)
Citric Acid monohydrate
Lemon Flavour (including Citropten, Citral, and ethanol)
Purified Water.

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

3 years.

6.4. Special precautions for storage

Keep bottle in the outer carton.
6.5. **Nature and contents of container**

Amber, transparent, non-plasticised PVC 60-ml bottle with aluminium pilfer proof screw cap fitted with polyethylene liner, equipped with a cover-cap to make it child resistant.

6.6. **Instruction for use and handling**

No special requirements.

7. **MARKETING AUTHORISATION HOLDER**

Regulatory Pharma Net s.r.l.
Corso Italia, 108
I-56125 PISA
Italy

8. **MARKETING AUTHORISATION NUMBER**

PL 20985/0003

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

13/04/2006

10. **DATE OF REVISION OF THE TEXT**

13/04/2006
EPTADONE ORAL SOLUTION (METHADONE HYDROCHLORIDE)  
PL 20985/0004

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

EPTADONE 1mg/ml oral solution.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each multidose container of 100ml and 1000ml of 1mg/ml contains 100mg and 1000mg methadone hydrochloride.

For excipients, see section 6.1

3. PHARMACEUTICAL FORM

Oral solution.

Clear liquid with lemon taste.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

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

For use as an analgesic for moderate to severe pain.

4.2. Posology and method of administration

For oral administration only.

<table>
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<tr>
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4.3. Contraindications

Hypersensitivity to the active substance or to any of the excipients.
Respiratory depression, obstructive airways disease, concurrent administration with MAO inhibitors or within 2 weeks of discontinuation of treatment with them.
Patients dependent on non-opioid drugs.
Use during an asthma attack is not recommended.
Use during labour is not recommended, the prolonged duration of action increases the risk of neonatal depression.
Methadone is not suitable for children.

4.4. Special warnings and precautions for use

Dependence. Methadone is a drug of addiction and is controlled under the Misuse of Drugs Act 1971 (Schedule 2).
Methadone can cause a morphine-like drug dependence. Following repeated administrations, psychic dependence, physical dependence and tolerance can occur, therefore it must be prescribed and administered with the same caution utilized for morphine.
Extreme caution must be taken in the following cases:
Cranial lesions and high intracranial pressure. The respiratory depressant effects of methadone and its capacity to increase the cerebrospinal fluid pressure can be considerably increased in the presence of an increase of the intracranial pressure; furthermore narcotics produce undesirable effects, that can hide neurological symptoms in patients with cranial lesions.
Asthma and other respiratory conditions. In patients with acute asthma attacks, in those with chronic obstructive pulmonary disease or cor pulmonare and in individuals with a substantially decreased respiratory reserve in pre-existing respiratory depression, hypoxia or hypercapnia, even the usual therapeutic dosages of narcotics may reduce the respiratory drive and increase the airway resistance to the point of apnoea.
Acute abdominal conditions. The use of methadone or other narcotics may
confound the diagnosis or the clinical course in patients with acute abdominal conditions.

**Hypotensive effect.** The administration of methadone can cause serious hypotension in hypovolemic subjects or with concomitant intake of medicinal products like phenothiazine or certain anaesthetics.

**Outpatient use.** In outpatients methadone may cause orthostatic hypotension.

**Use of narcotic antagonists.** In an individual with narcotic physical addiction, the administration of the usual dose of a narcotic antagonist can trigger an acute withdrawal syndrome. The severity of the syndrome will depend on the degree of physical dependence and on the dose of antagonist administered. The use of a narcotic antagonist in this subject should possibly be avoided. When this must be used for treatment of a severe respiratory depression in a patient physically addicted, the antagonist must be administered with extreme caution and gradually with dosages below the usual ones.

**Special risk patients.** Methadone must be administered with caution and the initial dose must be reduced in elderly and debilitated patients and patients with hypothyroidism, Addison’s disease, prostatic hypertrophy, urethral stricture. Caution should be exercised in patients with hepatic dysfunction or renal dysfunction.

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.

**Severe risk patients.** Suicide attempts with opiates, especially combined with tricyclic antidepressants, alcohol and other substances affecting the central nervous system, are part of the clinical features of dependency.

**Cardiac arrhythmia.** Since high doses of methadone have been associated with the occurrence of torsade de pointes (prolongation of the QT-interval), patients with risk factors for torsade de pointes should be treated with caution. The risk factors are:

- Electrolyte disorders, in particular hypokalaemia, hypocalcaemia and hypomagnesaemia.
- Congenital or acquired QT-prolongation.
- Cardiomyopathy, in particular in the presence of symptoms of cardiac failure.
- Sinus bradycardia.
- Symptomatic rhythm disorders.
- Concurrent medication known to prolong the QT-interval (in particular certain antiarrhythmics, neuroleptics, antibiotics, antidepressants and antihistaminics).

In patients for whom the potential benefits of a methadone-based treatment outweigh the risk of tachycardia onset, an electrocardiogram must be performed before therapy begins and after two weeks of treatment, with the aim of verifying and quantifying the effect of methadone hydrochloride on the QT interval. An electrocardiogram is also recommended before increasing the dose assumed.

**Sucrose.** Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

**EPTADONE contains small amount of ethanol, less than 100mg per 100ml.**
4.5. Interactions with other medicinal products and other forms of interaction

**Pharmacokinetic interactions**

**Inhibitors of P-glycoprotein:** methadone is a P-glycoprotein substrate, therefore all the drugs that inhibit it (quinidine, verapamil) can increase the serum concentration of methadone.

**CYP3A4 isoenzyme inducers:** the inducers of this isoenzyme (barbiturates, carbamazepine, phenytoin, nevirapine, rifampicin) can induce the hepatic metabolism, which could be more significant if the inducer is added after the methadone therapy has started. Following such interactions withdrawal symptom cases have been reported, therefore it was necessary to increase the dosage of methadone. When the CYP3A4 inducing drugs therapy is suspended, the dosage of methadone must be reduced.

**CYP3A4 isoenzyme inhibitors:** the interaction between metadone and cannabinoids (marijuana, hash, hemp, pot) has been proposed due to common CYP3A4 pathway. The interaction may result in altered or unpredictable metabolism. The interaction between clarithromycin and methadone as well as the interaction between erythromycin and methadone have been predicted due to the strong inhibition of CYP3A4 enzyme by erythromycin and clarithromycin. Clarithromycin and erythromycin may raise serum methadone level and/or increase methadone effects. The interaction between delavirdine and methadone has not been formally studied. It has been predicted due to the CYP3A4 inhibition by delavirdine, that may raise serum methadone level and/or increase methadone effects. Fluconazole has been shown to modify methadone kinetics in patients under methadone treatment. After 14 days of fluconazole 200 mg/day, serum methadone AUC and mean peak and trough concentrations increased by 35%, 27% and 48% respectively, while oral clearance was reduced by 24%. Although exposed to increased concentrations of methadone, patients exhibited neither signs of methadone overdose nor changes. The exact reason for this interaction is not fully understood, but a likely explanation is that fluconazole inhibits the metabolism of methadone because of its ability to inhibit several CYP enzymes, including CYP3A4 enzyme. The interaction between ketoconazole and methadone has been predicted due to CYP3A4 enzyme inhibition, that may raise serum methadone level and/or increase methadone effects. Because of extensive metabolism by the hepatic cytochrome P4503A4 system, itraconazole potentially interacts with drugs metabolized by this route. Itraconazole may decrease the elimination of drugs metabolized by CYP3A4 resulting in elevated plasma concentrations, which may prolong and/or increase both the therapeutic and the adverse effects of these drugs. Fluoxetine did not appear to alter the plasma methadone levels and no special precautions would therefore seem to be necessary if fluoxetine is added to methadone. Paroxetine is a strong CYP2D6 inhibitor; at a dosage of 20 mg/day, significantly increased (R)-methadone concentrations in a group of eight CYP2D6 extensive metabolisers by a mean value of 32%.

Fluvoxamine has been shown to increase the plasma concentrations of both enantiomers of methadone. The reason appears to be that fluvoxamine can inhibit
the liver metabolism of the methadone by cytochrome P450 isoenzyme CYP3A4, as confirmed by in vitro studies. The available information indicates that the effects of starting or stopping fluvoxamine should be monitored in patients on methadone, eventually adjusting the methadone dosage. Sertraline may inhibit methadone metabolism during the first few weeks of co-administration. Nefazodone is a potent inhibitor at CYP3A4 enzyme of the liver. No formal studies have been performed with co-administration of methadone and nefazodone, but an interaction has been predicted due to CYP3A4 enzyme inhibition, that may raise serum methadone level and/or increase methadone effects. Grapefruit Juice has a known inhibitory effect on CYP3A4 enzyme at intestinal level and P-glycoprotein. Juice administration is associated with a modest increase in methadone bioavailability, but it cannot be excluded that much stronger effect may occur in some patients, and thus grapefruit juice intake is not recommended during methadone treatment.

Didanosine and stavudine: methadone reduces the AUC and Cmax of didanosine and of stavudine, reducing the bioavailability of these drugs. Furthermore, methadone can slow down the absorption and increase the first passage metabolism of the aforementioned drugs.

Zidovudine: methadone increases the plasma concentration of zidovudine for both oral and intravenous administration, and also provokes an increase in the AUC of zidovudine for oral administration, more than for intravenous administration. Such effects are due to the inhibition of the glucuronidation of zidovudine and its reduced kidney clearance. During treatment with methadone, patients have to be monitored for a possible zidovudine toxicity, whereby it could be necessary to reduce the zidovudine dosage. The patients that take both drugs can develop typical symptoms of opioid withdrawal syndrome (headache, myalgia, fatigue and irritability).

Antiretroviral protease inhibitors: the antiretroviral protease inhibitors can inhibit the metabolism of methadone; the more significant reactions are obtained with ritonavir.

Abacavir: nineteen patients entering methadone treatment were given a single dose of abacavir (600 mg), begun methadone and, after 14 days, co-administered abacavir and methadone for the following 14 days. The results showed, in the last 14 days, a statistically significant increase (23%) in the rate of clearance of methadone, but no changes in the time to peak concentration or half-life. In addition, a significant decrease (34%) in the peak concentration and increase (67%) in the time to peak concentration of abacavir were observed in the first 14 days. The introduction of abacavir and amprenavir in 5 dependent patients in methadone treatment resulted in median decrease to 35% of the original concentration of methadone, with adverse effects compatible with withdrawal reactions in two patients.

Efavirenz: efavirenz induces the methadone metabolism through cytochrome P4503A4. Following a three-week therapy with efavirenz, the mean peak concentrations of methadone and the AUC were reduced by 48% and 57% respectively. Efavirenz added to a patient under methadone therapy could induce a withdrawal syndrome that usually starts after two weeks of efavirenz therapy, but can go on for up to 28 days. For this reason it may be necessary to adjust the methadone dosage.

Nevirapine: nevirapine induces methadone metabolism through cytochrome P450 family. The coadministration of nevirapine and methadone in twenty-five human
immunodeficiency virus-infected subjects significantly decreased the mean dose-adjusted AUC of methadone by 41%. Methadone dose adjustments are justified when methadone is coadministered with nevirapine.

**Urine acidifiers**: methadone is a weak base. Urine acidifiers (ammonium chloride) can increase methadone kidney clearance. In this situation the methadone dosage should be increased.

**Pharmacodynamic interactions**

**Opioid agonists/antagonists**: naloxone and naltrexone antagonise the methadone action and provoke a withdrawal syndrome. Butorphanol, nalbuphine and pentazocine can partially block the analgesia and increase the respiratory and central nervous system (CNS) depression due to methadone. These drugs used in combination with methadone can provoke and increase neurological, respiratory and hypotensive effects. The additive or antagonist effects depend on the methadone dosage and are more frequent when the methadone dosage is low or moderate. These drugs can cause withdrawal syndrome in patients on chronic therapy.

**CNS depressant**: drugs with a depressive action on the CNS can provoke an increase of respiratory depression, therefore it may be necessary to decrease the dosage of one or both drugs.

**Antidiarrhoeals**: the concomitant use of methadone and antidiarrhoeals (diphenoxylate and loperamide) can cause severe constipation and an increased depression of the CNS. Opioid analgesics, combined with antimuscarinic drugs can cause severe constipation or paralytic ileus, especially with chronic use.

**Octreotide**: can reduce the analgesic effect of methadone and morphine, therefore if a reduction or loss of pain control occurs octreotide suspension has to be taken into consideration.

**Alcohol**: may induce serious respiratory depression and hypotension.

### 4.6. Pregnancy and lactation

**Pregnancy**

There is no, or inadequate evidence of safety in human pregnancy. Female addicts who are pregnant will require specialised care from obstetric and paediatric staff with experience in such management. A careful risk benefit assessment should be made before administration to pregnant women. Possible adverse effects on the foetus and neonate include respiratory depression, low birth weight, neonatal withdrawal syndrome and increased rate of stillbirths. During labour there is a risk of gastric stasis and inhalation pneumonia in the mother.

**Lactation**

Methadone is excreted in breast milk and may cause respiratory depression in the newborn. Breast feeding is usually not recommended. However, a careful risk benefit assessment case by case is suggested, taking into account that methadone could prevent the possibility of an overdose syndrome in the newborn.
4.7. Effects on ability to drive and use machines

Patients should not drive or use machines while taking methadone. Methadone may cause drowsiness and reduce alertness and the ability to drive. 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

Respiratory Systems: From very common (≥ 1/10) to common (≥ 1/100, < 1/10): respiratory depression.
From uncommon (≥ 1/100, < 1/1000) to rare (≥ 1/10000, < 1/1000): respiratory arrest.
Central nervous system: From very common (≥ 1/10) to common (≥ 1/100, < 1/10): euphoria, dysphoria, weakness, headache, sedation, insomnia, agitation, disorientation, feeling of empty head, visual disturbances, dizziness, miosis.
Gastrointestinal tract and liver: From very common (≥ 1/10) to common (≥ 1/100, < 1/10): nausea, vomiting, constipation, xerostomia, anorexia and spasms of the biliary tract.
Cardiovascular apparatus: From very common (≥ 1/10) to common (≥ 1/100, < 1/10): rushing, bradycardia, palpitations, fainting, orthostatic hypotension and syncope.
From uncommon (≥ 1/100, < 1/1000) to rare (≥ 1/10000, < 1/1000): shock and cardiac arrest. Torsade de pointes can also occur with high doses.
Urinary-genital apparatus: From very common (≥ 1/10) to common (≥ 1/100, < 1/10): urinary retention and difficulty to urinate, anti-diuretic effect and libido reduction and/or sexual impotence.
Skin and Annexes: From very common (≥ 1/10) to common (≥ 1/100, < 1/10): excessive sweating, itchiness, nettle rash, other skin reactions, oedema. From uncommon (≥ 1/100, < 1/1000) to rare (≥ 1/10000, < 1/1000): hemorrhagic nettle rash.
Blood: From uncommon (≥ 1/100, < 1/1000) to rare (≥ 1/10000, < 1/1000): haemorrhagia
Endocrine Systems: From uncommon (≥ 1/100, < 1/1000) to rare (≥ 1/10000, < 1/1000): Long-term administration may produce raised prolactin levels.
Possible undesirable effects due to excipients: the medicinal product contains the following excipient that may cause undesirable effects: glycerol (harmful at high doses): may cause headache, stomach upset and diarrhoea.

4.9. Overdose

Symptoms and signs: similar to those for morphine. 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.

Treatment: treatment is supportive. Patients should be kept conscious wherever possible. 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.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: drugs used in opioid dependence
ATC code: N07BC02

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

Methadone is a basic and lipophilic drug, which is rapidly absorbed from the gastrointestinal tract with peak plasma levels between 1.5 and 3 h and an oral bioavailability of no less than 80%. Its pharmacokinetics are characterized by a rapid and extensive distribution phase followed by a slow elimination phase. The drug is subjected to considerable tissue distribution, yielding a relatively high volume of distribution and it is largely bound to plasma proteins (approximately...
89%). The sequestration of methadone at extravascular binding sites, followed by slow release into plasma, contributes to the prolonged duration of methadone half-life in plasma and urine. Pharmacokinetic studies in normal individuals, postoperative patients and methadone maintenance patients indicate that methadone has a variable (both within and among studies) terminal elimination half-life, with mean values ranging from 19 to 55 hours. Thus, there is potential for accumulation when methadone is administered at short intervals. The relative unpredictability of methadone pharmacokinetics renders difficult to devise a uniform dosing schedule and underlines the importance of individualized dosage. The oxidative biotransformation of methadone is the main route of drug elimination, which occurs primarily in the liver. In the first 96 h after administration, 15-60% can be recovered from the urine. The two major urinary metabolite lack pharmacological activity. Urinary pH is an important determinant of elimination half-life.

5.3. **Preclinical safety data**

Not applicable.

6. **PHARMACEUTICAL PARTICULARS**

6.1. **List of excipients**

Sucrose  
Glycerol  
Sodium Benzoate (E211)  
Citric Acid monohydrate  
Lemon Flavour (including Citropten, Citral, and ethanol)  
Purified Water.

6.2. **Incompatibilities**

Not applicable.

6.3. **Shelf life**

3 years. The solution should be used within 12 months of first use.

6.4. **Special precautions for storage**

Keep bottle in the outer carton (100ml container) or store in the original package (1000ml container).
6.5. Nature and contents of container

1. Amber, transparent, non-plasticised PVC 125-ml bottle with aluminium pilfer proof screw cap fitted with polyethylene liner, equipped with a cover-cap to make it child resistant.

2. Amber, transparent, non-plasticised PVC 1000-ml bottle with polypropylene pilfer proof screw cap fitted with polyethylene liner.

The presentations are equipped with a measuring cup for the administration of 5-10-15-20-25-30ml of oral solution.

6.6. Instruction for use and handling

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Regulatory Pharma Net s.r.l.
Corso Italia, 108
I-56125 PISA
Italy

8. MARKETING AUTHORISATION NUMBER

PL 20985/0004

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

13/04/2006

10 DATE OF REVISION OF THE TEXT

13/04/2006
SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

EPTADONE 5mg/ml oral solution

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each bottle contains 5mg/ml methadone hydrochloride in single dose bottles containing 100mg methadone hydrochloride

For excipients, see section 6.1

3. PHARMACEUTICAL FORM

Oral solution.

Clear liquid with lemon taste.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

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

4.2. Posology and method of administration

For oral administration only.

<table>
<thead>
<tr>
<th>Addiction</th>
<th>ADULTS.</th>
<th>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.</th>
</tr>
</thead>
<tbody>
<tr>
<td>ELDERLY.</td>
<td></td>
<td>In the case of the elderly or ill patients repeated doses should only be given with extreme caution.</td>
</tr>
<tr>
<td>CHILDREN.</td>
<td></td>
<td>Not recommended for children.</td>
</tr>
</tbody>
</table>
4.3. **Contraindications**

Hypersensitivity to the active substance or to any of the excipients.
Respiratory depression, obstructive airways disease, concurrent administration with MAO inhibitors or within 2 weeks of discontinuation of treatment with them.
Patients dependent on non-opioid drugs.
Use during an asthma attack is not recommended.
Use during labour is not recommended, the prolonged duration of action increases the risk of neonatal depression.
Methadone is not suitable for children.

4.4. **Special warnings and precautions for use**

Dependence. Methadone is a drug of addiction and is controlled under the Misuse of Drugs Act 1971 (Schedule 2).
Methadone can cause a morphine-like drug dependence. Following repeated administrations, psychic dependence, physical dependence and tolerance can occur, therefore it must be prescribed and administered with the same caution utilized for morphine.
Extreme caution must be taken in the following cases:
Cranial lesions and high intracranial pressure. The respiratory depressant effects of methadone and its capacity to increase the cerebrospinal fluid pressure can be considerably increased in the presence of an increase of the intracranial pressure; furthermore narcotics produce undesirable effects, that can hide neurological symptoms in patients with cranial lesions.
Asthma and other respiratory conditions. In patients with acute asthma attacks, in those with chronic obstructive pulmonary disease or cor pulmonare and in individuals with a substantially decreased respiratory reserve in pre-existing respiratory depression, hypoxia or hypercapnia, even the usual therapeutic dosages of narcotics may reduce the respiratory drive and increase the airway resistance to the point of apnoea.
Acute abdominal conditions. The use of methadone or other narcotics may confound the diagnosis or the clinical course in patients with acute abdominal conditions.
Hypotensive effect. The administration of methadone can cause serious hypotension in hypovolemic subjects or with concomitant intake of medicinal products like phenothiazine or certain anaesthetics.
Outpatient use. In outpatients methadone may cause orthostatic hypotension.
Use of narcotic antagonists. In an individual with narcotic physical addiction, the administration of the usual dose of a narcotic antagonist can trigger an acute withdrawal syndrome. The severity of the syndrome will depend on the degree of physical dependence and on the dose of antagonist administered. The use of a narcotic antagonist in this subject should possibly be avoided. When this must be used for treatment of a severe respiratory depression in a patient physically...
addicted, the antagonist must be administered with extreme caution and gradually with dosages below the usual ones.

**Special risk patients.** Methadone must be administered with caution and the initial dose must be reduced in elderly and debilitated patients and patients with hypothyroidism, Addison’s disease, prostatic hypertrophy, urethral stricture. Caution should be exercised in patients with hepatic dysfunction or renal dysfunction.

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.

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**Cardiac arrhythmia.** Since high doses of methadone have been associated with the occurrence of torsade de pointes (prolongation of the QT-interval), patients with risk factors for torsade de pointes should be treated with caution. The risk factors are:

- Electrolyte disorders, in particular hypokalaemia, hypocalcaemia and hypomagnesaemia.
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4.6. **Pregnancy and lactation**

**Pregnancy**

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**Lactation**

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From uncommon (≥ 1/100, < 1/1000) to rare (≥ 1/10000, < 1/10000): respiratory arrest.
Central nervous system: From very common (≥ 1/10) to common (≥ 1/100, < 1/10): euphoria, dysphoria, weakness, headache, sedation, insomnia, agitation, disorientation, feeling of empty head, visual disturbances, dizziness, miosis.
Gastrointestinal tract and liver: From very common (≥ 1/10) to common (≥ 1/100, < 1/10): nausea, vomiting, constipation, xerostomia, anorexia and spasms of the biliary tract.
Cardiovascular apparatus: From very common (≥ 1/10) to common (≥ 1/100, < 1/10): rushing, bradycardia, palpitations, fainting, orthostatic hypotension and syncope.
From uncommon (≥ 1/100, < 1/1000) to rare (≥ 1/10000, < 1/1000): shock and cardiac arrest. Torsade de pointes can also occur with high doses.
Urinary-genital apparatus: From very common (≥ 1/10) to common (≥ 1/100, < 1/10): urinary retention and difficulty to urinate, anti-diuretic effect and libido reduction and/or sexual impotence.
Skin and Annexes: From very common (≥ 1/10) to common (≥ 1/100, < 1/10): excessive sweating, itchiness, nettle rash, other skin reactions, oedema. From uncommon (≥ 1/100, < 1/1000) to rare (≥ 1/10000, < 1/1000): hemorrhagic nettle rash.
Blood: From uncommon (≥ 1/100, < 1/1000) to rare (≥ 1/10000, < 1/1000): haemorrhagia
Endocrine Systems: From uncommon (≥ 1/100, < 1/1000) to rare (≥ 1/10000, < 1/1000): Long-term administration may produce raised prolactin levels.
Possible undesirable effects due to excipients: the medicinal product contains the following excipient that may cause undesirable effects: glycerol (harmful at high doses): may cause headache, stomach upset and diarrhoea.

4.9. Overdose

Symptoms and signs: similar to those for morphine. 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.
Treatment: treatment is supportive. Patients should be kept conscious wherever possible. 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.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: drugs used in opioid dependence
ATC code: N07BC02
Methadone is a strong opioid agonist with actions predominantly at the μ receptor. The analgesic activity of the racemate is almost entirely due to the l-isomer, which is at least 10 times more potent as an analgesic than the d-isomer. The d-isomer lacks significant respiratory depressant activity but does have anti-tussive effects. Methadone also has some agonist actions at the 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

Methadone is a basic and lipophilic drug, which is rapidly absorbed from the gastrointestinal tract with peak plasma levels between 1.5 and 3 h and an oral bioavailability of no less than 80%. Its pharmacokinetics are characterized by a rapid and extensive distribution phase followed by a slow elimination phase. The drug is subjected to considerable tissue distribution, yielding a relatively high volume of distribution and it is largely bound to plasma proteins (approximately 89%). The sequestration of methadone at extravascular binding sites, followed by slow release into plasma, contributes to the prolonged duration of methadone half-life in plasma and urine. Pharmacokinetic studies in normal individuals, postoperative patients and methadone maintenance patients indicate that methadone has a variable (both within and among studies) terminal elimination half-life, with mean values ranging from 19 to 55 hours. Thus, there is potential for accumulation when methadone is administered at short intervals. The relative unpredictability of methadone pharmacokinetics renders difficult to devise a uniform dosing schedule and underlines the importance of individualized dosage. The oxidative biotransformation of methadone is the main route of drug elimination, which occurs
primarily in the liver. In the first 96 h after administration, 15-60% can be recovered from the urine. The two major urinary metabolite lack pharmacological activity. Urinary pH is an important determinant of elimination half-life.

5.3. Preclinical safety data

Not applicable.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Sucrose
Glycerol
Sodium Benzoate (E211)
Citric Acid monohydrate
Lemon Flavour (including Citropten, Citral, and ethanol)
Purified Water.

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

3 years.

6.4. Special precautions for storage

Keep bottle in the outer carton.

6.5. Nature and contents of container

Amber, transparent, non-plasticised PVC 25-ml bottle with aluminium pilfer proof screw cap fitted with polyethylene liner, equipped with a cover-cap to make it child resistant.

6.6. Instruction for use and handling

No special requirements.
7. MARKETING AUTHORISATION HOLDER

Regulatory Pharma Net s.r.l.
Corso Italia, 108
I-56125 PISA
Italy

8. MARKETING AUTHORISATION NUMBER

PL  20985/0005

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

13/04/2006

10. DATE OF REVISION OF THE TEXT

13/04/2006
EPTADONE ORAL SOLUTION (METHADONE HYDROCHLORIDE)
PL 20985/0006

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

EPTADONE 5mg/ml oral solution

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each multidose container of 1000ml of 5mg/ml contains 5000mg methadone hydrochloride

For excipients, see section 6.1

3. PHARMACEUTICAL FORM

Oral solution.

Clear liquid with lemon taste.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

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

4.2. Posology and method of administration

For oral administration only.

<table>
<thead>
<tr>
<th>Addiction</th>
<th>Prescription Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADULTS.</td>
<td>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.</td>
</tr>
<tr>
<td>ELDERLY.</td>
<td>In the case of the elderly or ill patients repeated doses should only be given with extreme caution.</td>
</tr>
<tr>
<td>CHILDREN.</td>
<td>Not recommended for children.</td>
</tr>
</tbody>
</table>
4.3. Contraindications

Hypersensitivity to the active substance or to any of the excipients.
Respiratory depression, obstructive airways disease, concurrent administration with MAO inhibitors or within 2 weeks of discontinuation of treatment with them.
Patients dependent on non-opioid drugs.
Use during an asthma attack is not recommended.
Use during labour is not recommended, the prolonged duration of action increases the risk of neonatal depression.
Methadone is not suitable for children.

4.4. Special warnings and precautions for use

Dependence. Methadone is a drug of addiction and is controlled under the Misuse of Drugs Act 1971 (Schedule 2).
Methadone can cause a morphine-like drug dependence. Following repeated administrations, psychic dependence, physical dependence and tolerance can occur, therefore it must be prescribed and administered with the same caution utilized for morphine.
Extreme caution must be taken in the following cases:
Cranial lesions and high intracranial pressure. The respiratory depressant effects of methadone and its capacity to increase the cerebrospinal fluid pressure can be considerably increased in the presence of an increase of the intracranial pressure; furthermore narcotics produce undesirable effects, that can hide neurological symptoms in patients with cranial lesions.
Asthma and other respiratory conditions. In patients with acute asthma attacks, in those with chronic obstructive pulmonary disease or cor pulmonare and in individuals with a substantially decreased respiratory reserve in pre-existing respiratory depression, hypoxia or hypercapnia, even the usual therapeutic dosages of narcotics may reduce the respiratory drive and increase the airway resistance to the point of apnoea.
Acute abdominal conditions. The use of methadone or other narcotics may confound the diagnosis or the clinical course in patients with acute abdominal conditions.
Hypotensive effect. The administration of methadone can cause serious hypotension in hypovolemic subjects or with concomitant intake of medicinal products like phenothiazine or certain anaesthetics.
Outpatient use. In outpatients methadone may cause orthostatic hypotension.
Use of narcotic antagonists. In an individual with narcotic physical addiction, the administration of the usual dose of a narcotic antagonist can trigger an acute withdrawal syndrome. The severity of the syndrome will depend on the degree of physical dependence and on the dose of antagonist administered. The use of a narcotic antagonist in this subject should possibly be avoided. When this must be used for treatment of a severe respiratory depression in a patient physically addicted, the antagonist must be administered with extreme caution and gradually
with dosages below the usual ones.

**Special risk patients.** Methadone must be administered with caution and the initial dose must be reduced in elderly and debilitated patients and patients with hypothyroidism, Addison’s disease, prostatic hypertrophy, urethral stricture. Caution should be exercised in patients with hepatic dysfunction or renal dysfunction.

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.

**Severe risk patients.** Suicide attempts with opiates, especially combined with tricyclic antidepressants, alcohol and other substances affecting the central nervous system, are part of the clinical features of dependency.

**Cardiac arrhythmia.** Since high doses of methadone have been associated with the occurrence of torsade de pointes (prolongation of the QT-interval), patients with risk factors for torsade de pointes should be treated with caution. The risk factors are:

- Electrolyte disorders, in particular hypokalaemia, hypocalcaemia and hypomagnesaemia.
- Congenital or acquired QT-prolongation.
- Cardiomyopathy, in particular in the presence of symptoms of cardiac failure.
- Sinus bradycardia.
- Symptomatic rhythm disorders.
- Concurrent medication known to prolong the QT-interval (in particular certain antiarrhythmics, neuroleptics, antibiotics, antidepressants and antihistaminics).

In patients for whom the potential benefits of a methadone-based treatment outweigh the risk of tachycardia onset, an electrocardiogram must be performed before therapy begins and after two weeks of treatment, with the aim of verifying and quantifying the effect of methadone hydrochloride on the QT interval. An electrocardiogram is also recommended before increasing the dose assumed.

**Sucrose.** Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

EPTADONE contains small amount of ethanol less than 100mg per 100ml.

### 4.5. Interactions with other medicinal products and other forms of interaction

**Pharmacokinetic interactions**

Inhibitors of P-glycoprotein: methadone is a P-glycoprotein substrate, therefore all the drugs that inhibit it (quinidine, verapamil) can increase the serum concentration of methadone.

**CYP3A4 isoenzyme inducers:** the inducers of this isoenzyme (barbiturates, carbamazepine, phenytoin, nevirapine, rifampicin) can induce the hepatic metabolism, which could be more significant if the inducer is added after the
methadone therapy has started. Following such interactions withdrawal symptom cases have been reported, therefore it was necessary to increase the dosage of methadone. When the CYP3A4 inducing drugs therapy is suspended, the dosage of methadone must be reduced.

CYP3A4 isoenzyme inhibitors: the interaction between methadone and cannabinoids (marijuana, hash, hemp, pot) has been proposed due to common CYP3A4 pathway. The interaction may result in altered or unpredictable metabolism. The interaction between clarithromycin and methadone as well as the interaction between erithromycin and methadone have been predicted due to the strong inhibition of CYP3A4 enzyme by erithomicyn and clarithromycin. Clarithromycin and erithromycin may raise serum methadone level and/or increase methadone effects. The interaction between delavirdine and methadone has not been formally studied. It has been predicted due to the CYP3A4 inhibition by delavirdine, that may raise serum methadone level and/or increase methadone effects. Fluconazole has been shown to modify methadone kinetics in patients under methadone treatment. After 14 days of fluconazole 200 mg/day, serum methadone AUC and mean peak and trough concentrations increased by 35%, 27% and 48% respectively, while oral clearance was reduced by 24 %. Although exposed to increased concentrations of methadone, patients exhibited neither signs of methadone overdose nor changes. The exact reason for this interaction is not fully understood, but a likely explanation is that fluconazole inhibits the metabolism of methadone because of its ability to inhibit several CYP enzymes, including CYP3A4 enzyme. The interaction between ketoconazole and methadone has been predicted due to CYP3A4 enzyme inhibition, that may raise serum methadone level and/or increase methadone effects. Because of extensive metabolism by the hepatic cytochrome P4503A4 system, itraconazole potentially interacts with drugs metabolized by this route. Itraconazole may decrease the elimination of drugs metabolized by CYP3A4 resulting in elevated plasma concentrations, which may prolong and/or increase both the therapeutic and the adverse effects of these drugs. Fluoxetine did not appear to alter the plasma methadone levels and no special precautions would therefore seem to be necessary if fluoxetine is added to methadone. Paroxetine is a strong CYP2D6 inhibitor; at a dosage of 20 mg/day, significantly increased (R)-methadone concentrations in a group of eight CYP2D6 extensive metabolisers by a mean value of 32%.

Fluvoxamine has been shown to increase the plasma concentrations of both enantiomers of methadone. The reason appears to be that fluvoxamine can inhibit the liver metabolism of the methadone by cytochrome P450 isoenzyme CYP3A4, as confirmed by in vitro studies. The available information indicates that the effects of starting or stopping fluvoxamine should be monitored in patients on methadone, eventually adjusting the methadone dosage. Sertraline may inhibit methadone metabolism during the first few weeks of co-administration. Nefazodone is a potent inhibitor at CYP3A4 enzyme of the liver. No formal studies have been performed with co-administration of methadone and nefazodone, but an interaction has been predicted due to CYP3A4 enzyme inhibition, that may raise serum methadone level and/or increase methadone effects. Grapefruit Juice has a known inhibitory effect on CYP3A4 enzyme at intestinal level and P-glycoprotein. Juice administration is associated with a modest increase in methadone bioavailability, but it cannot be excluded that much stronger effect may occur in some patients, and thus grapefruit juice intake is not recommended during methadone treatment.
Didanosine and stavudine: methadone reduces the AUC and Cmax of didanosine and of stavudine, reducing the bioavailability of these drugs. Furthermore, methadone can slow down the absorption and increase the first passage metabolism of the aforementioned drugs.

Zidovudine: methadone increases the plasma concentration of zidovudine for both oral and intravenous administration, and also provokes an increase in the AUC of zidovudine for oral administration, more than for intravenous administration. Such effects are due to the inhibition of the glucuronidation of zidovudine and its reduced kidney clearance. During treatment with methadone, patients have to be monitored for a possible zidovudine toxicity, whereby it could be necessary to reduce the zidovudine dosage. The patients that take both drugs can develop typical symptoms of opioid withdrawal syndrome (headache, myalgia, fatigue and irritability).

Antiretroviral protease inhibitors: the antiretroviral protease inhibitors can inhibit the metabolism of methadone; the more significant reactions are obtained with ritonavir.

Abacavir: nineteen patients entering methadone treatment were given a single dose of abacavir (600 mg), begun methadone and, after 14 days, co-administered abacavir and methadone for the following 14 days. The results showed, in the last 14 days, a statistically significant increase (23%) in the rate of clearance of methadone, but no changes in the time to peak concentration or half-life. In addition, a significant decrease (34%) in the peak concentration and increase (67%) in the time to peak concentration of abacavir were observed in the first 14 days. The introduction of abacavir and amprenavir in 5 dependent patients in methadone treatment resulted in median decrease to 35% of the original concentration of methadone, with adverse effects compatible with withdrawal reactions in two patients.

Efavirenz: efavirenz induces the methadone metabolism through cytochrome P4503A4. Following a three-week therapy with efavirenz, the mean peak concentrations of methadone and the AUC were reduced by 48% and 57% respectively. Efavirenz added to a patient under methadone therapy could induce a withdrawal syndrome that usually starts after two weeks of efavirenz therapy, but can go on for up to 28 days. For this reason it may be necessary to adjust the methadone dosage.

Nevirapine: nevirapine induces methadone metabolism through cytochrome P450 family. The coadministration of nevirapine and methadone in twenty-five human immunodeficiency virus-infected subjects significantly decreased the mean dose-adjusted AUC of methadone by 41%. Methadone dose adjustments are justified when methadone is coadministered with nevirapine.

Urine acidifiers: methadone is a weak base. Urine acidifiers (ammonium chloride) can increase methadone kidney clearance. In this situation the methadone dosage should be increased.

Pharmacodynamic interactions

Opioid agonists/antagonists: naloxone and naltrexone antagonise the methadone action and provoke a withdrawal syndrome.

Butorphanol, nalbuphine and pentazocine can partially block the analgesia and increase the respiratory and central nervous system (CNS) depression due to
methadone. These drugs used in combination with methadone can provoke and increase neurological, respiratory and hypotensive effects. The additive or antagonist effects depend on the methadone dosage and are more frequent when the methadone dosage is low or moderate. These drugs can cause withdrawal syndrome in patients on chronic therapy.

**CNS depressant**: drugs with a depressive action on the CNS can provoke an increase of respiratory depression, therefore it may be necessary to decrease the dosage of one or both drugs.

**Antidiarrhoeals**: the concomitant use of methadone and antidiarrhoeals (diphenoxylate and loperamide) can cause severe constipation and an increased depression of the CNS. Opioid analgesics, combined with antimuscarinic drugs can cause severe constipation or paralytic ileus, especially with chronic use.

**Octreotide**: can reduce the analgesic effect of methadone and morphine, therefore if a reduction or loss of pain control occurs octreotide suspension has to be taken into consideration.

**Alcohol**: may induce serious respiratory depression and hypotension.

### 4.6. Pregnancy and lactation

**Pregnancy**

There is no, or inadequate evidence of safety in human pregnancy. Female addicts who are pregnant will require specialised care from obstetric and paediatric staff with experience in such management. A careful risk benefit assessment should be made before administration to pregnant women. Possible adverse effects on the foetus and neonate include respiratory depression, low birth weight, neonatal withdrawal syndrome and increased rate of stillbirths. During labour there is a risk of gastric stasis and inhalation pneumonia in the mother.

**Lactation**

Methadone is excreted in breast milk and may cause respiratory depression in the newborn. Breast feeding is usually not recommended. However, a careful risk benefit assessment case by case is suggested, taking into account that methadone could prevent the possibility of an overdose syndrome in the newborn.

### 4.7. Effects on ability to drive and use machines

Patients should not drive or use machines while taking methadone. Methadone may cause drowsiness and reduce alertness and the ability to drive. 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

**Respiratory Systems**: From very common (≥ 1/10) to common (≥ 1/100, < 1/10):
respiratory depression.
From uncommon (≥ 1/100, < 1/1000) to rare (≥ 1/10000, < 1/1000): respiratory arrest.
Central nervous system: From very common (≥ 1/10) to common (≥ 1/100, < 1/10): euphoria, dysphoria, weakness, headache, sedation, insomnia, agitation, disorientation, feeling of empty head, visual disturbances, dizziness, miosis.
Gastrointestinal tract and liver: From very common (≥ 1/10) to common (≥ 1/100, < 1/10): nausea, vomiting, constipation, xerostomia, anorexia and spasms of the biliary tract.
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From uncommon (≥ 1/100, < 1/1000) to rare (≥ 1/10000, < 1/1000): shock and cardiac arrest. Torsade de pointes can also occur with high doses.
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Blood: From uncommon (≥ 1/100, < 1/1000) to rare (≥ 1/10000, < 1/1000): haemorrhagia
Endocrine Systems: From uncommon (≥ 1/100, < 1/1000) to rare (≥ 1/10000, < 1/1000): Long-term administration may produce raised prolactin levels.
Possible undesirable effects due to excipients: the medicinal product contains the following excipient that may cause undesirable effects: glycerol (harmful at high doses): may cause headache, stomach upset and diarrhoea.

4.9. Overdose

Symptoms and signs: similar to those for morphine. 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.
Treatment: treatment is supportive. Patients should be kept conscious wherever possible. 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.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: drugs used in opioid dependence
ATC code: N07BC02
Methadone is a strong opioid agonist with actions predominantly at the µ receptor. The analgesic activity of the racemate is almost entirely due to the l-isomer, which is at least 10 times more potent as an analgesic than the d-isomer. The d-isomer lacks significant respiratory depressant activity but does have anti-tussive effects. Methadone also has some agonist actions at the 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.

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Methadone is a basic and lipophilic drug, which is rapidly absorbed from the gastrointestinal tract with peak plasma levels between 1.5 and 3 h and an oral bioavailability of no less than 80%. Its pharmacokinetics are characterized by a rapid and extensive distribution phase followed by a slow elimination phase. The drug is subjected to considerable tissue distribution, yielding a relatively high volume of distribution and it is largely bound to plasma proteins (approximately 89%). The sequestration of methadone at extravascular binding sites, followed by slow release into plasma, contributes to the prolonged duration of methadone half-life in plasma and urine. Pharmacokinetic studies in normal individuals, postoperative patients and methadone maintenance patients indicate that methadone has a variable (both within and among studies) terminal elimination half-life, with mean values ranging from 19 to 55 hours. Thus, there is potential for accumulation when methadone is administered at short intervals. The relative unpredictability of methadone pharmacokinetics renders difficult to devise a uniform dosing schedule and underlines the importance of individualized dosage. The oxidative biotransformation of methadone is the main route of drug elimination, which occurs primarily in the liver. In the first 96 h after administration, 15-60% can be
recovered from the urine. The two major urinary metabolite lack pharmacological activity. Urinary pH is an important determinant of elimination half-life.

5.3. Preclinical safety data

Not applicable.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Sucrose
Glycerol
Sodium Benzoate (E211)
Citric Acid monohydrate
Lemon Flavour (including Citropten, Citral, and ethanol)
Purified Water.

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

3 years. The solution should be used within 12 months of first use.

6.4. Special precautions for storage

Store in the original package.

6.5. Nature and contents of container

Amber, transparent, non-plasticised PVC 1000-ml bottle with polypropylene pilfer proof screw cap fitted with polyethylene liner.

The presentation is equipped with a measuring cup for the administration of 1-2-3-4-5-6 ml of oral solution.

6.6. Instruction for use and handling

No special requirements.
7. MARKETING AUTHORISATION HOLDER

Regulatory Pharma Net s.r.l.
Corso Italia, 108
I-56125 PISA
Italy

8. MARKETING AUTHORISATION NUMBER

PL 20985/0006

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

13/04/2006

10. DATE OF REVISION OF THE TEXT

13/04/2006
PRODUCT INFORMATION LEAFLET

Read all of this leaflet carefully before you start taking this medicine.
- Keep this leaflet. You may need to read it again.
- If you have further questions, please ask your doctor or your pharmacist.
- This medicine has been prescribed for you personally and you should not pass it on to others. It may harm them, even if their symptoms are the same as yours.

In this leaflet:
1. What EPTADONE is and what it is used for
2. Before you take EPTADONE
3. How to take EPTADONE
4. Possible side effects
5. Strong EPTADONE
6. Further information

EPTADONE 1 mg/ml oral solution, Methadone hydrochloride
- The active ingredient is methadone hydrochloride. Each 1ml contains 1mg Methadone hydrochloride.
- The other ingredients are sucrose, glycol, citric acid and monohydrate, lemon flavour including Citron, Cirtal, and elmantol, sodium benzoate and purified water.

Marketing Authorisation Holder:
Regulatory Pharma Net s.r.l.
Cone India 108
1-50125 PISA
Italy

Manufacturer:
L. Micelli & C. del Fil. Alli d’Istituto di Scienze di Baumllo S.p.A
Strada Statutaria 1, Fras. Garuzzinari
50068 Scandicci (FI)
Italy

1. WHAT EPTADONE IS AND WHAT IT IS USED FOR

Eptadone is an oral solution. It is used as a substitute for addictive drugs or in the control of pain.

It is available in the following packs:
- 1mg/ml oral solution in 20ml single-dose container. Each bottle contains 20mg methadone hydrochloride.
- 1mg/ml oral solution in 60ml single-dose container. Each bottle contains 60mg methadone hydrochloride.
- 1mg/ml oral solution in 200ml multidose container. Each bottle contains 200mg methadone hydrochloride.
- 1mg/ml oral solution in 1000ml multidose container, with measuring cup. Each bottle contains 1000mg methadone hydrochloride.

Eptadone is used in the treatment of opioid drug addiction.
Eptadone is also used in the treatment of moderate to severe pain.

2. BEFORE YOU TAKE EPTADONE

Do not take EPTADONE:
- If you are hypersensitive (allergic) to methadone hydrochloride or any of the other ingredients of EPTADONE;
- If you have an addiction to non-opioid drugs;
- If you have a respiratory ailment;
- If you have heart or angina pectoris;
- If you have taken monoamine oxidase inhibitors or have taken them within the last two weeks;
- If you are going into labour or are in labour.

NOTE: children must not be given this medicine.

Take special care with EPTADONE:
- If you have kidney disease;
- If you have liver disease;
- If you are suffering from severe headache or have recently suffered a head injury;
- If you have raised pressure within your skull;
- If you are suffering from heart disease especially with heart beating alterations;
- If you are suffering from low blood pressure;
- If you are suffering from shock (or circulatory failure);
- If you are suffering from endocrine thyroid gland;
- If you are suffering from hypercortical adrenal gland;
- If you are a man who suffers from prostate problems;
- If you are elderly;
- If you are ill;
- If you are taking any of the following medicines:
  - antibiotics (erythromycin, clindamycin, ciprofloxacin)
  - antihistamines (promethazine, cimetidine, metoclopramide)
  - anticonvulsants (carbamazepine, phenytoin, sodium valproate)
  - antimuscarinics (diphenoxylate and loperamide)
  - tranquilisers and antidepressants (fluoxetine, paroxetine, sertraline, nefazodone and fluvoxamine)
  - other sedatives e.g. amino acid.
  - strong painkillers e.g. morphine
  - naloxone
  - naltrexone
  - buprenorphine
  - nalbuphine
  - ondansetron
  - omeprazole
  - cimetidine, ranitidine, cannabinoids.
- you have been told your doctor that you have an intolerance to some sugars.

Taking EPTADONE with food and drinks:
You should not take alcohol or drink grapefruit juice whilst taking this medicine.

Pregnancy
Ask your doctor for advice before taking any medicine.
You should not take EPTADONE if you are going into labour or are in labour.

Breastfeeding:
Ask your doctor for advice before taking any medicine. During breast feeding some methadone will pass on to the baby via the milk. This may be permissible if your doctor considers it safe in your particular circumstances.

Driving and using machines:
EPTADONE will severely affect your ability to drive and use machines, whilst taking it and for some time afterwards. After taking methadone, the time after which it is safe to resume these activities is variable. Consult your doctor about your own situation.

Important information about some of the ingredients of EPTADONE:
If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product.
EPTADONE contains 40g of sucrose per 100ml! This should be taken into account in patients with diabetes mellitus.
EPTADONE contains a small amount of ethanol (alcohol), less than 100mg per 100ml.
EPTADONE contains glycerol, at the highest dosages, it may cause headache, stomach upset and diarrhoea.

Taking other medicines:
Please inform your doctor or pharmacist if you are taking or have recently taken any other medicines, even those not prescribed.

3. HOW TO TAKE EPTADONE
Always take EPTADONE exactly as your doctor has instructed you. You should check with your doctor or pharmacist if you are unsure.
Do not take more or less than the stated dose. Do not take it more or less than prescribed.
Do not take it for a longer time than your doctor prescribed.
EPTADONE is to be taken by mouth.

Addition:
ADULTS: The usual dose is initially 10-20mg per day increasing to 40-60mg per day as necessary. The dose should be taken as prescribed by your doctor.

If you are elderly or very ill, you should be careful when taking repeated doses.

Pain
ADULTS: The usual dose is 5 to 10mg every 6-8 hours.

You should be careful when taking repeated doses, especially if you are elderly or very ill.

EPTADONE is not recommended for children.

If you have the impression that the effect of EPTADONE is too strong or too weak, talk to your doctor or pharmacist.

If you take more EPTADONE than you should:
Immediately contact a doctor or a hospital if you take too much. Symptoms of an overdose include:
- difficulty in breathing;
- extreme drowsiness or even stupor or coma;
- very small pupils;
- cold and clammy skin;
- a very slow pulse rate;
- muscle weakness.
In extreme cases, breathing or blood flow may stop and a heart attack may occur.

If you forget to take EPTADONE:
If you miss a dose, do not take this medicine when you remember. Wait until the next dose is due then take only one dose. Do not double the dose.

Effects when treatment with EPTADONE is stopped:
Do not stop taking EPTADONE suddenly as withdrawal symptoms may occur. Your doctor will gradually stop the medicine when necessary.

4. POSSIBLE SIDE EFFECTS
Like all medicines, EPTADONE can have side effects. These may include nausea (feeling sick), vomiting (being sick), constipation, excessive sweating, increased pressure inside the brain, particularly in patients who already have this condition, difficulty in breathing, worsening of existing asthma, increased levels in the blood of a hormone called prolactin, low blood pressure and orthostatic hypotension (temporary fall in blood pressure on standing causing dizziness). Other possible side effects include: difficulty in sleeping, restlessness, irritability or changes in mood, feeling of empty head, weakness, drowsiness, confusion, visual disturbances, rash (eruption or blisters), diarrhoea, dry mouth, loss of appetite, decrease in heart rate, accelerated heart beats, palpitations, facial flushing, difficulty in passing urine, abdominal pain (caused by tension in the tissues that carry urine to the bladder and into the intestines), loss of libido and/or sexual impotence, itching, haemorrhage. You may notice that some of the side effects become less severe over time.

If you notice any side effects not mentioned in this leaflet, please inform your doctor or pharmacist.

5. STORING EPTADONE
Keep bottle in the outer carton (20ml, 40ml, 60ml and 100 ml container) or store in the original package (1000ml).

Keep out of the reach and sight of children.
Do not use this medicine after the expiry date (month, year) stated on the container.

RETURN ANY UNUSED OR EXPIRED MEDICINE TO YOUR DOCTOR OR PHARMACIST FOR SAFE DISPOSAL.

6. FURTHER INFORMATION
For any information about this medicinal product, please contact the Marketing Authorisation Holder.

This leaflet was prepared in
EPTADONE ORAL SOLUTION (METHADONE HYDROCHLORIDE)
PL 20985/0004

PRODUCT INFORMATION LEAFLET – 1000ML MULTIDOSE BOTTLE

Read all of this leaflet carefully before you start taking this medicine.
- Keep this leaflet. You may need to read it again.
- If you have further questions, please ask your doctor or your pharmacist.
- This medicine has been prescribed for you personally and you should not pass it on to others. It may harm them, even if their symptoms are the same as yours.

In this leaflet:
1. What EPTADONE is and what it is used for
2. Before you take EPTADONE
3. How to take EPTADONE
4. Possible side effects
5. Storing EPTADONE
6. Further information

EPTADONE 1 mg/ml oral solution, Methadone hydrochloride

- The active ingredient is methane hydrochloride. Each 1ml contains 1mg Methadone hydrochloride.
- The other ingredients are: sucrose, glycerol, citric acid monohydrate, lemon flavour (including Citron, Citral, and ethanol), sodium benzoate and purified water.

Marketing Authorisation Holder:
Regulatory Pharma S.r.l.
Consile street, 108
Add. 25 Pisa
Italy

Manufacturer:
L’Arienti & C. srl Abbott Sede di Esercizio SpA
Strada Stabile 67, Frascati, Rome
00016 Italy

1. WHAT EPTADONE IS AND WHAT IT IS USED FOR

Eptadone is an oral solution. It is used as a substitute for addictive drugs or in the control of pain.

It is available in the following pack sizes:
- 1 mg/ml oral solution in 20ml single-dose containers. Each bottle contains 20mg methadone hydrochloride.

2. BEFORE YOU TAKE EPTADONE

Do not take EPTADONE:
- If you are hypersensitive (allergic) to methadone hydrochloride or any of the other ingredients of EPTADONE;
- If you have an addiction to non-opioid drugs;
- If you have a respiratory ailment;
- If you have had or are having difficulty in breathing;
- If you are taking Monoamine Oxidase Inhibitors or have taken them within the last two weeks;
- If you are going into labour or are in labour,

NOTE: children must not be given this medicine.

Take special care with EPTADONE:
- If you have kidney disease;
- If you have liver disease;
- If you are suffering from severe headache or have recently suffered a head injury;
- If you have raised pressure within your skull;
- If you are suffering from heart diseases especially with heart beating alterations;
- If you are suffering from low blood pressure;
- If you are suffering from shock (circulatory failure);
- If you are suffering from underactive thyroid gland;
- If you are a man who suffers from prostate problems;
- If you are elderly;
- If you are ill;
- If you are taking any of the following medicines: antibacterials (rifampicin, clarithromycin, erythromycin), antifungals (fluconazole, itraconazole, ketoconazole) and corticosteroids (budesonide,

Pregnancy
Ask your doctor for advice before taking any medicine. You should not take EPTADONE if you are going into labour or are in labour.

Breast feeding
Ask your doctor for advice before taking any medicine. During breast feeding some medicines will pass on to the baby via the milk. This may be permissible if your doctor considers it safe in your particular circumstances.

Driving and using machines:
EPTADONE will severely affect your ability to drive and use machines, whilst taking it and for some time afterwards. After taking methadone, the time after which it is safe to resume these activities is variable. Consult your doctor about your own situation.

Important information about some of the ingredients of EPTADONE:
If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product. EPTADONE contains 40g of sucrose per 100ml. This should be taken into account in patients with diabetes mellitus.
EPTADONE contains a small amount of ethanol (alcohol), less than 100mg per 100ml.

EPTADONE contains glycerol at the highest dosages. It may cause headache, stomach upset and diarrhoea.

Taking other medicines:
Please inform your doctor or pharmacist if you are taking or have recently taken any other medicines, even those not prescribed.

3. HOW TO TAKE EPTADONE

Always take EPTADONE exactly as your doctor has instructed you. You should check with your doctor or pharmacist if you are unsure.

Do not take more or less than the stated dose. Do not take it more or less often than prescribed.

Do not take it for a longer time than your doctor prescribed.

EPTADONE is to be taken by mouth.

Addiction

ADULTS. The usual dose is initially 10-20mg per day increasing to 40-60mg per day as necessary. The dose should be taken as prescribed by your doctor.

If you are elderly or very ill, you should be careful when taking repeated doses.

Pain

ADULTS. The usual dose is 5 to 10mg, every 4-6 hours.

You should be careful when taking repeated doses, especially if you are elderly or very ill.

EPTADONE is not recommended for children.

If you have the impression that the effect of EPTADONE is too strong or too weak, talk your doctor or pharmacist.

If you take more EPTADONE than you should:
Immediately contact a doctor or a hospital if you take too much. Symptoms of an overdose include:
- difficulty in breathing;
- extreme drowsiness or even stupor or coma;

- very small pupils;
- cold and clammy skin;
- a very slow pulse rate;
- muscle weakness.

In extreme cases, breathing or blood flow may stop and a heart attack may occur.

If you forget to take EPTADONE:
If you miss a dose, do not take this medicine when you remember. Wait until the next dose is due then take only one dose. Do not double the dose.

Effects when treatment with EPTADONE is stopped:
Do not stop taking EPTADONE suddenly as withdrawal symptoms may occur. Your doctor will gradually stop the medicine when necessary.

4. POSSIBLE SIDE EFFECTS

Like all medicines, EPTADONE can have side effects. These may include nausea (feeling sick), vomiting (being sick), constipation, excessive sweating, increased pressure inside the brain, particularly in patients who already have this condition, difficulty in breathing, worsening of existing asthmatic, increased levels in the blood of a hormone called prolactin, low blood pressure and orthostatic hypotension (temporary fall in blood pressure on standing causing dizziness). Other possible side effects include: difficulty in sleeping, restlessness, irritability or changes in mood, feeling of empty head, weakness, drowsiness, confusion, visual disturbances, paresthesia (a sensation of the paresthesia, dry mouth, loss of appetite, decrease in heart rate, accelerated heart beats, palpitations, facial flushing, difficulty in passing urine, abdominal pain (caused by tension in the tissues that carry urine to the bladder and bowels to the intestines) loss of libido and/or sexual impotence, itching, haemorrhage.

You may notice that some of the side effects become less severe with time.

If you notice any side effects not mentioned in this leaflet, please inform your doctor or pharmacist.

5. STORING EPTADONE

Keep bottle in the outer carton (20ml, 40ml, 60ml and 100ml container) or store in the original package (1000ml). Keep out of the reach and sight of children.

Do not use this medicine after the expiry date (month, year) stated on the container.

Once the bottle is opened, use EPTADONE 1mg/ml oral solution 100ml and

100ml multi-dose container within 12 months.

RETURN ANY UNUSED OR EXPIRED MEDICINE TO YOUR DOCTOR OR PHARMACIST FOR SAFE DISPOSAL.

6. FURTHER INFORMATION

For any information about this medicinal product, please contact the Marketing Authorisation Holder.

This leaflet was prepared in
EPTADONE ORAL SOLUTION (METHADONE HYDROCHLORIDE)
PL 20985/0005

PRODUCT INFORMATION LEAFLET

Read all of this leaflet carefully before you start taking this medicine.
- Keep this leaflet. You may need to read it again.
- If you have further questions, please ask your doctor or your pharmacist.
- This medicine has been prescribed for you personally and you should not pass it on to others. It may harm them, even if their symptoms are the same as yours.

In this leaflet:
1. What EPTADONE is and what it is used for
2. Before you take EPTADONE
3. How to take EPTADONE
4. Possible side effects
5. Storing EPTADONE
6. Further information

EPTADONE 5 mg/ml oral solution, Methadone hydrochloride
- The active ingredient is methadone hydrochloride. Each 5 ml contains 5 mg methadone hydrochloride.
- The other ingredients are sucrose, glycerol, citric and monohydric acid, lemon flavour (including Citroxin, Citral, and ethyl), sodium benzoate and purified water.

Marketing Authorisation Holder:
Regulatory Pharma No.115.D
Costa Italia 106
80125 Pisa
Italy

Manufacturer:
L. Melotti & C. srl E. F. A. S. Spa Società Esercizio SPA
Strada Stabile 57, Frat. Guastalla
6016 Scardov (R)
Italy

1. WHAT EPTADONE IS AND WHAT IT IS USED FOR
Eptadone is an oral solution. It is used as a substitute for addictive drugs.
- It is available in the following forms:
  - 5 mg/ml oral solution in 20 ml single-dose container. Each bottle contains 100 mg methadone hydrochloride.
  - 5 mg/ml oral solution in 1000 ml multidose container, with measuring cup. Each bottle contains 6000 mg.

Eptadone 5 mg/ml oral solution is used in the treatment of opioid drug addiction.

2. BEFORE YOU TAKE EPTADONE
Do not take EPTADONE:
- if you are hypersensitive (allergic) to methadone hydrochloride or any of the other ingredients of EPTADONE;
- if you have an addiction to non-opioid drugs;
- if you have kidney problems;
- if you have breast problems;
- if you are suffering from a severe headache or have recently suffered a head injury;
- if you have raised blood pressure within the past year;
- if you are suffering from heart disease especially with heart beating alterations;
- if you are suffering from low blood pressure;
- if you are suffering from heart attack (coronary artery disease);
- if you are suffering from osteoporotic hypercalcinemia;
- if you are suffering from hyperparathyroidism;
- if you are a man who suffer from prostate problems;
- if you are elderly;
- if you are fat;
- if you are taking any of the following medicines:
  - anticonvulsants (topiramate, carbamazepine, lamotrigine)
  - antimicrobial (flucloxacillin, tiamazacillin, imipenem)
  - anticoagulants (warfarin, phenprocoumon, clopidogrel)
  - antidepressants (clomipramine and fenfluramine)
  - tranquillizers and sedatives (alprazolam, paroxetine, alprazolam, nitrazepam, and fluvoxamine)
  - strong analgesics e.g. morphine
  - naltrexone
  - buprenorphine
  - buprenorphine
  - naltrexone
  - pentazocine
  - codeine
  - quinidine, aspirin, cannabinoids
- you have been told your doctor that you have an intolerance to some sugars.

Taking EPTADONE with food and drink:
You should not take alcohol or drink grapefruit juice whilst taking this medicine.
Pregnancy
Ask your doctor for advice before taking any medicine. You should not take EPTADONE if you are going into labour or are in labour.

Breastfeeding
Ask your doctor for advice before taking any medicine. During breast feeding some methadone will pass on to the baby via the milk. This may be permissible if your doctor considers it safe in your particular circumstances.

Driving and using machines:
EPTADONE will severely affect your ability to drive and use machines, whilst taking it and for some time afterwards. After taking methadone, the time after which it is safe to resume these activities is variable. Consult your doctor about your own situation.

Important Information about some of the Ingredients of EPTADONE:
If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product.

EPTADONE contains 8g of sucrose at the highest dosage (100mg). This should be taken into account in patients with diabetes mellitus.

EPTADONE contains a small amount of ethanol (alcohol), less than 100mg per 100ml.

Taking other medicines:
Please inform your doctor or pharmacist if you are taking or have recently taken any other medicines, even those not prescribed.

3. HOW TO TAKE EPTADONE
Always take EPTADONE exactly as your doctor has instructed you. You should check with your doctor or pharmacist if you are unsure.
Do not take more or less than the stated dose. Do not take it more or less often than prescribed.
Do not take it for a longer time than your doctor prescribed.

EPTADONE is to be taken by mouth:

ADULTS. The usual dose is initially 10-20mg per day (corresponding to 2-4ml oral solution) increasing to 40-60mg per day (corresponding to 8-12ml oral solution) as necessary. The dose should be taken as prescribed by your doctor.

If you are elderly or very ill, you should be careful when taking repeated doses.

EPTADONE is not recommended for children.

If you have the impression that the effect of EPTADONE is too strong or too weak, talk to your doctor or pharmacist.

If you take more EPTADONE than you should:
Immediately contact a doctor or a hospital if you take too much. Symptoms of an overdose include:
- difficulty in breathing;
- extreme drowsiness or even stupor or coma;
- very small pupils;
- cold and clammy skin;
- a very slow pulse rate;
- muscle weakness.

In extreme cases, breathing or blood flow may stop and a heart attack may occur.

If you forget to take EPTADONE:
If you miss a dose, do not take this medicine when you remember. Wait until the next dose is due then take only one dose. Do not double the dose.

Effects when treatment with EPTADONE is stopped:
Do not stop taking EPTADONE suddenly as withdrawal symptoms may occur. Your doctor will gradually stop the medicine when necessary.

4. POSSIBLE SIDE EFFECTS
Like all medicines, EPTADONE can have side effects. These may include nausea (feeling sick), vomiting (being sick), constipation, excessive sweating, increased pressure inside the brain, particularly in patients who already have this condition, difficulty in breathing, worsening of existing asthma, increased levels in the blood of the hormone cortisol, low blood pressure and orthostatic hypotension (temporary fall in blood pressure on standing causing dizziness). Other possible side effects include: difficulty in sleeping, restlessness, irritability or changes in mood, feeling of empty head, weakness, drowsiness, confusion, visual disturbances, miosis (constriction of the pupil), dizziness, dry mouth, loss of appetite, decrease in heart rate, accelerated heart rate, palpitations, facial flushing, difficulty in passing urine, abdominal pain (caused by tension in the tissues that carry urine to the bladder and bile to the intestine), loss of libido and/or sexual impotence, itching, haemorrhage.

You may notice that some of the side effects become less severe with time.

If you notice any side effects not mentioned in this leaflet, please inform your doctor or pharmacist.

5. STORING EPTADONE
Keep bottle in the outer carton (20ml container) or store in the original package (100ml). Keep out of the reach and sight of children.
Do not use this medicine after the expiry date (month, year) stated on the container.
Once the bottle is opened use EPTADONE 5mg/ml oral solution 100ml multidose container within 12 months.
RETURN ANY UNILSED OR EXPIRED MEDICINE TO YOUR DOCTOR OR PHARMACIST FOR SAFE DISPOSAL.

6. FURTHER INFORMATION
For any information about this medicinal product, please contact the Marketing Authorisation Holder.

This leaflet was prepared in

MHRA PAR - EPTADONE Oral Solution (Methadone Hydrochloride) - 86 -
PL 20985/0001-6
EPTADONE ORAL SOLUTION (METHADONE HYDROCHLORIDE) PL 20985/0006

PRODUCT INFORMATION LEAFLET

Read all of this leaflet carefully before you start taking this medicine.
- Keep this leaflet. You may need to read it again.
- If you have further questions, please ask your doctor or pharmacist.
- This medicine has been prescribed for you personally and you should not pass it on to others. It may harm them, even if their symptoms are the same as yours.

In this leaflet:
1. What EPTADONE is and what it is used for
2. Before you take EPTADONE
3. How to take EPTADONE
4. Possible side effects
5. Storing EPTADONE
6. Further information

EPTADONE 5 mg/ml oral solution, Methadone hydrochloride

- The active ingredient is methadone hydrochloride. Each 1 ml contains 5 mg Methadone hydrochloride.
- The other ingredients are: sucrose, citric acid monohydrate, lemon flavour (including Citronel, Ogal, and ethanol), sodium benzoate and purified water.

Marketing Authorisation Holder:
Regulatory Pharma M. S. L.
Corso Italia, 136
16152 Genoa
Italy

Manufacturer:
M. Menini & C. de Fil Mini Societa di Esercito Spa
Strada Statale 27, Prazzi, Granara
59018 Scandicci (FI)
Italy

1. WHAT EPTADONE IS AND WHAT IT IS USED FOR

Eptadone is an oral solution. It is used as a substitute for addictive drugs.

It is available in the following packs:
- 5mg/ml oral solution in 50ml single-dose container. Each bottle contains 100mg methadone hydrochloride

2. BEFORE YOU TAKE EPTADONE

Do not take EPTADONE:
- If you are hypersensitive (allergy) to methadone hydrochloride or any of the other ingredients of EPTADONE;
- If you have an addiction to non-opioid drugs;
- If you have a respiratory ailment;
- If you have had or are having difficulty in breathing;
- If you are taking Monoamine Oxidase Inhibitors or have taken them within the last two weeks;
- If you are going into labour or are in labour.

NOTE: children must not be given this medicine.

Take special care with EPTADONE:
- If you have kidney disease;
- If you have liver disease;
- If you are suffering from severe headache or have recently suffered a head injury;
- If you have raised pressure within your skull;
- If you are suffering from heart diseases especially with heart beating alterations;
- If you are suffering from low blood pressure;
- If you are suffering from shock (circulatory failure);
- If you are suffering from unproductive thyroid gland;
- If you are suffering from hypertensive cerebral gland;
- If you are a man who suffers from prostatic problems;
- If you are elderly;
- If you are ill;
- If you are taking any of the following medicines: antibiotics (amoxicillin, clarithromycin, erythromycin, and tetracycline), fluconazole, itraconazole, ketoconazole, anticonvulsants (barbiturates, phenytoin, carbamazepine, antiarrhythmic drugs (digoxin, lidocaine, and verapamil), tricyclic antidepressants (flouxetine, paroxetine, sertraline, mirtazapine, tramadol and fluoxetine) amine oxidases e.g. amphetamine, dexamfetamine, phenelzine, selegiline, amphetamine, mazindol, dexamfetamine, tramadol, and fluoxetine), benzodiazepines e.g. diazepam, oxazepam, and alprazolam.

Driving and using machines:
EPTADONE will severely affect your ability to drive and use machines, whilst taking it and for some time afterwards. After taking methadone, the time after which it is safe to resume these activities is variable. Consult your doctor about your own situation.

Important information about some of the ingredients of EPTADONE:
If you have been told by your doctor that you have an intolerance to some sugars.

Taking EPTADONE with food and drink:
You should not take alcohol or drink grapefruit juice whilst taking this medicine.

Pregnancy
Ask your doctor for advice before taking any medicine. You should not take EPTADONE if you are going into labour or are in labour.

Breast feeding
Ask your doctor for advice before taking any medicine. During breast feeding some methadone will pass on to the baby via the milk. This may be permissible if your doctor considers it safe in your particular circumstances.

Driving and using machines:
EPTADONE will severely affect your ability to drive and use machines, whilst taking it and for some time afterwards. After taking methadone, the time after which it is safe to resume these activities is variable. Consult your doctor about your own situation.

Important information about some of the ingredients of EPTADONE:
If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product.

EPTADONE contains 5g of sucrose at the highest dosage (100mg). This should be taken into account in patients with diabetes mellitus.
EPTADONE contains a small amount of alcohol (alcohol), less than 10mg per 100ml.

Taking other medicines:
Please inform your doctor or pharmacist if you are taking or have recently taken any other medicines, even those not prescribed.
3. HOW TO TAKE EPTADONE

Always take EPTADONE exactly as your doctor has instructed you. You should check with your doctor or pharmacist if you are unsure.

Do not take more or less than the stated dose. Do not take it more or less often than prescribed.

Do not take it for a longer time than your doctor prescribed.

EPTADONE is to be taken by mouth.

ADULTS: The usual dose is initially 10-20mg per day (corresponding to 2-4ml oral solution) increasing to 40-60mg per day (corresponding to 8-12ml oral solution) as necessary. The dose should be taken as prescribed by your doctor.

If you are elderly or very ill, you should be careful when taking repeated doses.

EPTADONE is not recommended for children.

If you have the impression that the effect of EPTADONE is too strong or too weak, talk your doctor or pharmacist.

If you take more EPTADONE than you should:

Immediately contact a doctor or a hospital if you take too much. Symptoms of an overdose include:

- difficulty in breathing;
- extreme drowsiness or even stupor or coma;
- very small pupils;
- cold and clammy skin;
- a very slow pulse rate;
- muscle weakness.

In extreme cases, breathing or blood flow may stop and a heart attack may occur.

If you forget to take EPTADONE:

If you miss a dose, do not take this medicine when you remember. Wait until the next dose is due then take only one dose. Do not double the dose.

Effects when treatment with EPTADONE is stopped:

Do not stop taking EPTADONE suddenly as withdrawal symptoms may occur. Your doctor will gradually stop the medication when necessary.

4. POSSIBLE SIDE EFFECTS

Like all medicines, EPTADONE can have side effects. These may include nausea (feeling sick), vomiting (being sick), constipation, excessive sweating, increased pressure inside the brain, particularly in patients who already have this condition, difficulty in breathing, worsening of existing asthma, increased levels in the blood of a hormone called prolactin, low blood pressure and orthostatic hypotension (temporary fall in blood pressure on standing causing dizziness). Other possible side effects include: difficulty in sleeping, restlessness, irritability or changes in mood, feeling of empty head, weakness, drowsiness, confusion, visual disturbances, miss (constriction of the pupils), dizziness, dry mouth; loss of appetite, decrease in heart rate, accelerated heart beats, palpitations, facial flushing, difficulty in passing urine, abdominal pain (caused by tension in the tissues that carry urine to the bladder and bile to the intestines), loss of fluids and/or sexual impotence, itching, haemorrhage. You may notice that some of the side effects become less severe with time.

If you notice any side effects not mentioned in this leaflet, please inform your doctor or pharmacist.

5. STORING EPTADONE

Keep bottle in the outer carton (20ml container) or store in the original package (100ml).

Keep out of the reach of and sight of children.

Do not use this medicine after the expiry date (month, year) stated on the container.

Once the bottle is opened, use EPTADONE 5mg/ml oral solution 1000ml multi-dose container within 12 months.

RETURN ANY UNUSED OR EXPIRED MEDICINE TO YOUR DOCTOR OR PHARMACIST FOR SAFE DISPOSAL.

6. FURTHER INFORMATION

For any information about this medicinal product, please contact the Marketing Authorisation Holder.

This leaflet was prepared in

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MHRA PAR - EPTADONE Oral Solution (Methadone Hydrochloride) - 88 -
PL 20985/0001-6
EPTADONE ORAL SOLUTION (METHADONE HYDROCHLORIDE)
PL 20985/0002

LABELLING

CONTAINER

BOTTLE

Composition: Each 1 ml of oral solution contains: Methadone hydrochloride 1 mg
Excipients: sucrose, ethanol.

Method of administration: Read the package leaflet before use. Keep out of the reach and sight of children. Keep bottle in the outer carton.

MHRA PAR - EPTADONE Oral Solution (Methadone Hydrochloride) - 90 -
PL 20985/0001-6
100ML MULTIDOSE BOTTLE

EPTADONE 1mg/ml oral solution
Methadone hydrochloride

1000 ml

Composition: Each 1 ml of oral solution contains:
Methadone hydrochloride 1mg
Excipients: sucrose, ethanol,
See leaflet for further information
Oral solution
1000-ml multidose container
Method of administration: read the package leaflet before use.

KEEP OUT OF THE REACH AND SIGHT OF CHILDREN
STORE IN THE ORIGINAL PACKAGE.
RETURN ANY UNUSED OR EXPIRED MEDICINE TO YOUR DOCTOR OR PHARMACIST FOR SAFE DISPOSAL.
UK Marketing Authorisation Holder
Regulatory Pharma Net s.r.l.
Corso Italia, 108 - I-56125 PISA - Italy

POM
PL 20985/0004

MHRA PAR - EPTADONE Oral Solution (Methadone Hydrochloride) - 93 -
PL 20985/0001-6
EPTADONE ORAL SOLUTION (METHADONE HYDROCHLORIDE)
PL 20985/0006

LABELLING

1000ML MULTIDOSE BOTTLE

EPTADONE 5mg/ml oral solution
Methadone hydrochloride

1000 ml

Composition: Each 1 ml of oral solution contains:
Methadone hydrochloride 5mg
Excipients: sucrose, ethanol.
See leaflet for further information.

Oral solution
1000-ml multidose container

Method of administration: read the package leaflet before use.
KEEP OUT OF THE REACH AND SIGHT OF CHILDREN.
STORE IN THE ORIGINAL PACKAGE.
RETURN ANY UNUSED OR EXPIRED MEDICINE TO YOUR
DOCTOR OR PHARMACIST FOR SAFE DISPOSAL.
UK Marketing Authorisation Holder
Regulatory Pharma Net s.r.l.
Corso Italia, 108 - I-56125 PISA - Italy
POM
PL 20985/0006