



Public Assessment Report

from the Norwegian Medicines Agency

Metadon oral solution 1 mg/ml and 5 mg/ml
A/S Den norske Eterfabrikk, Norway

MA-number in Norway: 04-2423, 04-2424

Date: 2007-09-25

This assessment report is published by the Norwegian Medicines Agency (NoMA) following Article 21 (3) and (4) of Directive 2001/83/EC. The report comments on the registration dossier which was submitted to the NoMA and its fellow organisations in all concerned EEA member states. It reflects the scientific discussion between the NoMA and all concerned member states at the end of the evaluation process and provides a summary of the grounds for approval and issue of a marketing authorisation.

This assessment report will be updated by an addendum whenever new important information becomes available.

- Module 1: Information about the initial procedure
- Module 2: Summary of product Characteristics (SPC)
- Module 3: Package Leaflet
- Module 4: Labelling
- Module 5: Scientific discussion
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Module 1: Information about the initial procedure:

1. Type of application: Well-established use application according to Directive 2001/83/EC as amended, Article 10a.
2. Active substance: methadone hydrochloride
3. Pharmaceutical form: oral solution
4. Strength: 1 mg/ml and 5 mg/ml
5. MA holder: A/S Den norske Eterfabrikk, Oslo, Norway
6. Reference Member State: Norway
7. Concerned Member States: Sweden
8. Procedure-number: : NO/H/0124/001-002/MR
9. Timetable:
Start (Day 0): 04.04.2007
End (Day 90): 03.07.2007

Module 2: Summary of product Characteristics (SPC)

1. NAME OF THE MEDICINAL PRODUCT

Metadon DnE 1mg/ml oral solution.
Metadon DnE 5 mg/ml oral solution.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Metadon DnE 1 mg/ml oral solution:
Methadone hydrochloride 1mg/ml

Metadon DnE 5 mg/ml oral solution:
Methadone hydrochloride 5 mg/ml.

Excipients: ethanol 24 mg/ml (equivalent to the alcohol concentration in light beer)
Methyl parahydroxybenzoate.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Oral solution.

A clear, colourless liquid with an odour of fruit.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Substitution therapy in patients dependent on opioids concomitant with medical and psychological treatment and social rehabilitation.

4.2 Posology and method of administration

For oral use only. To be used undiluted.

The dosage should be determined and adjusted to the individual patient.

In general the initial dose will be between 10-30mg. In cases where tolerance to opioids is high, the normal initial dose will be between 25-40 mg. In reaching the maintenance treatment it is recommended that the dose is increased by maximum 10 mg at a time. The majority of individuals in maintenance treatment will require 60-120 mg per day for an effective and safe treatment, some may however need a higher dosage. The dosage should be determined based upon the clinical evaluation. Methadone should normally be administered once per 24 hours. If administered more frequently than once per 24 hours there will be a danger of accumulation and overdose.

The patient must be observed after administration in the beginning of the dose-increase so that unintended reactions can be observed. The patient has increasing serum-level in up to two hours, and it is important that reactions of overdose or other dangerous/inconvenient reactions are discovered.

Some patients develop auto-induction, so that metabolism is increased. In such cases it is necessary to increase the dose one or more times to maintain optimal effect.

If a patient has previously been administered a combined agonist/antagonist treatment (e.g. buprenorphine), the dose should be reduced gradually during the introduction of methadone. When the methadone treatment is discontinued and a transition to sublingual buprenorphine (especially if combined with naloxone) is planned, the methadone dose should initially be reduced to 30 mg/day to avoid withdrawal distress induced by buprenorphine/naloxone.

When the treatment is to be discontinued, this should be done with a gradual dose reduction. Further, reference is made to National Guidelines for methadone treatment.

Methadone shall not be given to children.

4.3 Contraindications

Respiratory depression. Hypersensitivity to methadone or to any of the excipients.

4.4 Special warnings and special precautions for use

Methadone DnE is for oral administration only. The medicinal product must not be injected. Heroin abusers, at an early stage of their drug career, should not be given methadone maintenance treatment.

Methadone can produce drug dependence of the morphine type, although the methadone abstinence syndrome differs from morphine in that the onset is slower, the course is more prolonged, and the symptoms less severe.

Special precautions for use of methadone are as for use of opioids in general.

Acute asthmatic attack, chronic obstructive pulmonary disease or cor pulmonale, decreased respiratory reserve, hypoxia, or hypercapnia are relative contraindications, the individual case must be evaluated separately.

Caution should be exercised when used concomitantly with MAO-inhibitors and in two weeks after such treatment.

Methadone should be used with caution and in reduced dosage in patients who are concomitantly using other narcotic analgesics, general anaesthetics, phenothiazines, other tranquillisers, sedative-hypnotics, tricyclic antidepressants, and other CNS depressants (including alcohol) (see 4.5 Interactions with other medicinal products and other forms of interaction).

Methadone should be given with caution and with reduced initial dose to elderly as well as to patients with: impaired renal function, abrupt changes in hepatic status, hypothyroidism, Addison's disease, prostatic hypertrophy, or urethral stricture.

Cases of QT-prolongation and "torsade de pointes" has been reported in connection with methadone treatment, especially when administered in high doses. Methadone should be administered with care to patients potentially at risk of developing QT prolongation, e.g. when: previous arrhythmias, severe cardiac disease or ischemic heart disease, a family history of sudden death at young age, electrolyte anomalies (hypokalaemia, hypomagnesemia), concomitant treatment with medicinal drugs with a potential of prolongation of the QT interval, concomitant treatment with medicinal products known to cause electrolyte anomalies and concomitant treatment with cytochrome P450 CYP 3A4 antagonists (see section 4.5).

ECG monitoring should be considered in patients with known risk of developing QT prolongation, especially in women.

Methyl parahydroxybenzoate may cause allergic reactions (possibly delayed).

The oral solution contains 2.3 % ethanol, equivalent to the alcohol concentration in light beer.

4.5 Interaction with other medicinal products and other forms of interaction

P-glycoprotein inhibitors:

Methadone is a substrate of P-glycoprotein; all medicinal substances that inhibit P-glycoprotein (e.g. quinidine, verapamil) may therefore increase the serum concentrations of methadone. The pharmacodynamic effect of methadone may also increase because of improved passage over the blood brain barrier.

Since the main metabolic pathway of methadone is CYP 3A4 drug interactions can be expected. Serum methadone levels can be reduced by the concomitant use of drugs such as carbamazepine, phenobarbital, phenytoin, rifampicin, nevirapine, efavirenz dexamethasone, *Hypericum perforatum* (St John's wort) and cocaine. For example, after three weeks treatment with 600 mg efavirenz daily, the mean maximal concentration and exposure decreased by 48 % and 57 % respectively, in patients treated with methadone (35-100 mg daily). The consequences of enzyme induction become more striking if the inducer is administered after the treatment with methadone has been initiated. An increase in methadone dosage may be needed to prevent the development of withdrawal symptoms. If treatment with a CYP3A4 inducer is discontinued, the dose of methadone may have to be reduced.

Concomitant treatment of HIV infection:

Certain protease inhibitors (amprenavir, nelfinavir, lopinavir/ritonavir and ritonavir/saquinavir) seem to be able to decrease the serum levels of methadone. For ritonavir administered alone, a doubling in the AUC for methadone has been shown.

Zidovudine (a nucleoside analogue) inhibits the metabolism of methadone. Methadone can reduce AUC and peak drug concentrations (C_{max}) for didanosine and stavudine, primarily due to decreased bioavailability. It is suggested to increase didanosine dose when used in combination with methadone.

Certain antibiotics (clarithromycin, erythromycine, telithromycin), azole antimycotics, (e.g. ketoconazole, itraconazole, fluconazole), nefazodone, fluoxetine, fluvoxamine, paroxetine and sertraline inhibit the metabolism of methadone. This results in an increase in the serum levels of methadone. A 40-100% increase in the methadone plasma level/dose ratio has been shown when used together with fluvoxamine. If these substances are prescribed to patients receiving maintenance treatment of methadone, one should be aware of the risk of overdose.

Methadone can double the serum levels of desipramine.

Methadone should not be co-administered with medicinal drugs with a potential of prolongation of the QT interval such as antiarrhythmics (sotalol, amiodarone, flecainide), antipsychotics (thioridazine, haloperidol, sertindole) or antibiotics (erythromycine, clarithromycine).

Methadone should be used with caution and in reduced dosage in patients who are concurrently receiving other narcotic analgesics, general anaesthetics, phenothiazines, other tranquillisers, sedative-hypnotics, tricyclic antidepressants, and other CNS depressants (including alcohol), since respiratory depression, hypotension, and profound sedation or coma may be the result.

Caution should be exercised when used concomitantly with MAO-inhibitors and in two weeks after treatment with irreversible MAO inhibitors.

4.6 Pregnancy and lactation

Pregnancy: Limited data on the use of methadone in pregnancy in humans show no elevated risk of congenital abnormalities. Withdrawal symptoms/respiratory depression may occur in neonates of mothers that were treated with methadone chronically during pregnancy. Data from animal studies have shown reproduction toxicity (see 5.3). It is generally advisable not to detoxify the patient, especially after the 20th week of pregnancy,. If possible the Methadone dose should be reduced just before and during birth due to the risk of neonatal respiratory depression.

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

4.7 Effects on ability to drive and use machines

Methadone influence psychomotoric functions until the patient is stabilised on a suitable level. The patient should therefore not drive or use machines until the patient has been stable and with no sign of drug abuse for the last 6 months. When the patient is capable of driving and using machines varies from person to person, and shall be decided by the physician. Further, reference is made to National Guidelines for methadone treatment.

The content of alcohol (approx 2.3 %) must be taken into consideration, especially if large volumes are to be taken.

4.8 Undesirable effects

The major side effects of methadone are respiratory depression. This can occur during the stabilisation phase. Respiratory arrest, shock, and cardiac arrest have occurred.

The most frequently observed adverse reactions include;

Gastrointestinal disorders: Constipation, weight gain, nausea and vomiting.

Psychiatric disorders: Euphoria.

Nervous system disorders: Dizziness and sedation.

Skin and subcutaneous tissue disorders: Transient skin rash.

General disorders and administration site conditions: Fluid retention and sweating.

Other adverse effects include the following:

Psychiatric disorders: Dysphoria and agitation.

Nervous system disorders: Weakness, headache, insomnia, disorientation and visual disturbances.

Gastrointestinal disorders: Dry mouth, anorexia and constipation.

Hepatobiliary disorders: Biliary tract spasms.

Vascular disorders: Flushing of the face and fainting.

Cardiac disorders: Bradycardia and palpitation. Cases of QT-prolongation and "torsade de pointes" has been reported in connection with methadone treatment, especially when administered in high doses.

Renal and urinary disorders: Urinary retention and antidiuretic effect.

Reproductive system and breast disorders: Reduced libido and/or potency and amenorrhoea.

Skin and subcutaneous tissue disorders: Pruritus, urticaria, other skin rashes, oedema, and rarely hemorrhagic urticaria.

During prolonged administration of methadone, as in a methadone maintenance treatment programme, there is a gradual, yet progressive disappearance of side effects over a period of several weeks. However, constipation and sweating often persist. Review studies have shown that methadone maintenance treatment has extremely few side effects, included shown to be non-sedative.

Prolonged use of methadone may lead to dependence of the morphine type. The withdrawal symptoms are similar to, but less intense and more prolonged, than those produced by morphine or diamorphine (heroin).

4.9 Overdose

Symptoms: Serious overdose of methadone 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 serious cases of overdose, especially in cases of intravenous administration, there can occur apnoea, cardiovascular deficiency, cardiovascular stop and death.

Treatment: Primary attention should be given to open airways and reestablishment of adequate respiratory exchange. Opioid antagonists may be necessary, but since methadone has a long duration of action (36-48 hours), and the most widely used antagonist, naloxone only 1-3 hours, the treatment with such a short-acting antagonists should be repeated if necessary. An antagonist should not be given if there are no clinical signs of respiratory depression or danger for loss of consciousness. Administration of an antagonist to patients who are physically dependent on narcotics will give acute withdrawal symptoms. Use of antagonists to such patients should be avoided - if possible - and reserved for cases with serious respiratory depression. Then administration should be done with great caution.

Very little methadone is removed by peritoneal dialysis or haemodialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Farmacotherapeutic group: Drugs in opioid dependencency.

ATC-code: N07B C02.

Methadone is a synthetic potent competitive opioid agonist, which like morphine and heroine, acts mainly on the μ -receptors, which are believed to be particularly important for analgesia, euphoria, respiratory depression, tolerance and dependence. Other mechanism of action involve autonome functions such as intestine motility, cough reflexes, sweating and tonus in smooth muscles. The principle actions of therapeutic value are analgesia and sedation, detoxification or maintenance in narcotic effect.

Since methadone is a competitive agonist with a strong affinity towards μ -receptors, intake of methadone will reduce the effect of other opioids like heroin.

Methadone in therapeutic oral doses does not give subjective euphoria or clinical behavioural changes.

5.2 Pharmacokinetic properties

Absorption: Methadone is rapidly absorbed following oral administration. Methadone can be detected in plasma within 30 minutes after oral ingestion; and reaches peak concentrations in about 4 hours.

Distribution: Methadone is widely distributed in the tissues, diffuses across the placenta, and is excreted in breast milk.

Protein binding: approx. 90 %.

Metabolism: Methadone is metabolised in the liver to inactive metabolites by several cytochrome P-450 enzyme systems, most important is CYP 3A4, and thus pharmacokinetic interactions are expected and do occur. The major metabolite is 2-ethylidine-1,5-dimethyl-3,3-diphenyl-pyrrolidine(EDDP).

Elimination: The metabolites are excreted in the urine and the bile together with unchanged drug. The amount of methadone excreted in the urine is increased with increasing acidity of the urine.

The half-life of methadone has been estimated to be 24 to 36 hours, with considerable variations across individuals (10-80 hours). Women can have shorter half-lives than men.

5.3 Preclinical safety data

Methadone at high doses caused birth abnormalities in marmots, hamsters and mice, in which most reports were of exencephaly and defects in the central nervous system. Rachischis in the cervical

region was found occasionally in mice. Non-closure of the neural tube was found in chicken embryos. Methadone was not teratogenic in rats and rabbits. Also a reduced number of young was found in rats and increased mortality, growth retardation, neurological behavioural effects and reduced brain weight were found in the pups. Reduced ossification of the digits, sternum and skull was found in mice and a smaller number of foetuses per litter.

No carcinogenicity studies have been carried out.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Methyl parahydroxybenzoate

Ethanol

Sodium citrate

Citric acid, anhydrous

Saccharin sodium

Masking flavour

Blackcurrant/apple flavour

Purified water

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

18 months.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

1 mg/ml oral solution is supplied in 50 ml, 100 ml or 150 ml brown plastic bottles (PET):

Pack sizes: 15 ml, 20 ml, 25 ml, 30 ml, 35 ml, 40 ml, 45 ml, 50 ml, 55 ml, 60 ml, 65 ml, 70 ml, 75 ml, 80 ml, 85 ml, 90 ml, 95 ml, 100 ml, 110 ml, 120 ml, 130 ml, 140 ml and 150 ml.

5 mg/ml oral solution is supplied in 50 ml brown plastic bottles (PET):

Pack sizes: 14 ml, 16 ml, 18 ml, 20 ml, 22 ml, 24 ml, 26 ml, 28 ml, 30 ml, 32 ml, 34 ml, 36 ml, 38 ml, 40 ml, 42 ml, 44 ml, 46 ml, 48 ml and 50 ml.

Methadone DnE oral solution will be supplied with child-resistant, tamper evident screw-cap; PP closure with LDPE liner.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7. MARKETING AUTHORISATION HOLDER

A/S Den norske Eterfabrikk

Eterveien 12
PO Box 10, Bøler
0620 Oslo
Norway

8. MARKETING AUTHORIZATION NUMBER

9. DATE OF FIRST AUTHORIZATION/RENEWAL OF THE AUTHORIZATION

10. DATE REVISION OF THE TEXT

July 3, 2007

Module 3: Package Leaflet

PACKAGE LEAFLET: INFORMATION FOR THE USER

Metadon DnE 1 mg/ml oral solution
Metadon DnE 5 mg/ml oral solution
Methadone hydrochloride

Read all of this leaflet carefully before you start using this medicine.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. What Metadon DnE is and what it is used for
2. Before you use Metadon DnE
3. How to use Metadon DnE
4. Possible side effects
5. How to store Metadon DnE
6. Further information

1. WHAT METADON DNE IS AND WHAT IT IS USED FOR

Please be aware that the doctor may have prescribed this medicine for another use and/or with another dose than given in the leaflet. Always use the medicine as prescribed and written on the pharmacy label.

Metadon DnE is used for treatment of patients that has become dependent of agents in the group called opioids. Treatment should be performed concomitantly with medical, psychological and social follow-up.

2. BEFORE YOU USE METADON DNE

Do not use Metadon DnE

- if you are allergic (hypersensitive) to methadone hydrochloride or any of the other ingredients of Metadon DnE. See section 6. Further information
- if you have severe respiratory problems

Take special care with Metadon DnE

- if you have an acute asthma attack or reduced lung capacity due to a lung disease
- if you have severely impaired renal function
- if you have had abrupt changes in liver values, hypothyroidism, Addison's disease, enlargement of prostate or narrowed urether
- if you have certain types of changes in you heart rhythm or other severe heart disease

You must be careful if you are using alcohol when you are treated with Metadon DnE.

Using other medicines

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

Tell your doctor if you are using the following drugs as these may give a reduced effect of methadone: antiepileptic drugs (like carbamazepine, phenobarbitale, phenytoine) or antibiotics (of the type rifampicin, telithromycin or erythromycine) or agents against virus (such as amprenavir, nelfinavir, nevirapin, efivarenc) and herb products containing St John's wort.

Tell your doctor if you are using any of the following medicinal products as these may increase the level of methadone in your blood: agents against fungus (like ritonavir and zidovudine), agents for heart diseases (verapamil, quinidine) or some agents against depression (so called MAO inhibitors, fluoxetine, fluvoxamine, paroxetine and sertraline).

Methadone should not be combined with drugs that affect the heart rhythm (such as sotalol, amiodarone and flecainide) or with some agents used for psychiatric diseases (thioridazine, haloperidole, sertindole) and some antibiotics (erythromycine, clarithromycine).

Caution should be exercised when you are at the same time having other strong pain killers, agents for psychic diseases (of the type phenothiazines), tranquillisers, hypnotics or other agents that affects the central nervous system

Pregnancy

It might be that the foetus can be affected. Ask your doctor for advice before taking Metadon DnE if you are pregnant.

Breast-feeding

It might be that the nursing child can be affected. Ask your doctor for advice before taking Metadon DnE if you are breast-feeding.

Driving and using machines

Do not drive a car or operate any tools or machines until you have been stable on your treatment for a longer period. Your doctor will decide when you may start driving. You should only drive a car or perform risky work when it is safe for you. Drugs can affect your ability to drive a car or perform risky work. Read this leaflet carefully. If you are in doubt ask your doctor or pharmacist.

Important information about some of the ingredients of Metadon DnE

The oral solution contains 2.3 % ethanol, equivalent to the alcohol content in light beer.

The oral solution also contains methyl parahydroxybenzoate which may cause allergic reactions (possibly delayed).

3. HOW TO USE METADON DNE

Always use Metadon DnE exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

The dose is individual and the doctor adjusts it especially for you. Metadon DnE is an oral liquid (solution), which is to be swallowed.

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

If you take use more Metadon DnE than you should

Symptoms of a dose too high, is difficulties in breathing, extreme sleepiness that can develop into coma.

Contact doctor, hospital or a Poison Information Centre if you have taken too much drug or if children have taken this drug by accident. For other questions about the drug, contact your doctor or a pharmacy.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Metadon DnE can cause side effects, although not everybody gets them.

The most common side effects are constipation and sweating.

The following side effects are common during the start of the treatment, but they usually pass gradually over a period of some weeks:

increase of weight, nausea and vomiting, in high spirit, dizziness and sleepiness, transient skin rash, fluid-retention.

Other side effects might be: low spirit, agitation, weakness, headache, sleeping-problems, agitation, disorientation, dry mouth, anorexia, spasms of the biliary tract, flushing of the face, fainting, rapid heartbeat, palpitation of the heart. Some cases of rhythm disturbances are reported, especially with high doses of methadone. Urinary retention, reduced libido and/or potency, disturbances in the menstruation cycle, rash, urticaria, other skin rash.

The most severe side effect is difficulties in breathing. This may occur in the beginning until the right dose is found.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or a pharmacist.

5. HOW TO STORE METADON DNE

Keep out of the reach and sight of children. This medicinal product does not require any special storage conditions regarding temperature or light.

Do not use Metadon DnE after the expiry date which is stated on the label. The expiry date refers to the last day of that month.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Metadon DnE contains

- The active substance is methadone hydrochloride; 1 mg/ml and 5 mg/ml
- The other ingredients are methyl parahydroxybenzoate, ethanol (96 %) 24 mg/ml, sodium citrate, citric acid anhydrous, saccharin sodium, masking flavouring blackcurrant/apple flavour, purified water.

What Metadon DnE looks like and contents of the pack

Metadon DnE oral solution, (liquid) comes in brown plastic bottles with childproof and tamperproof twist-off cap.

Pack sizes: 1 mg/ml: 15ml, 20ml, 25ml, 30ml, 35ml, 40ml, 45ml, 50ml, 55ml, 60ml, 65ml, 70ml, 75ml, 80ml, 85ml, 90ml, 95ml, 100ml, 110ml, 120ml, 130ml, 140ml, 150ml.

5 mg/ml: 14ml, 16ml, 18ml, 20ml, 22ml, 24ml, 26ml, 28ml, 30ml, 32ml, 34ml, 36ml, 38ml, 40ml, 42ml, 44ml, 46ml, 48ml, 50ml. Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

A/S Den norske Eterfabrikk
P.O. Box 10, Bøler, 0620 Oslo, Norway

This leaflet was last approved in 07/2007.

Module 4: Labelling

Not attached

Module 5: Scientific discussion

This module reflects the scientific discussion for the approval of Metadon DnE oral solution 1 mg/ml and 5 mg/ml. The procedure was finalised at 03.07.2007 (on Day 90). For information on changes after this date please refer to the module 'Update'.

I INTRODUCTION

Based on review of the submitted data, the Member States have granted a marketing authorisation (MA) for Metadon DnE oral solution 1 mg/ml and 5 mg/ml from A/S Den norske Eterfabrikk. The first date of authorisation was 6. April 2005 in Norway. The product is approved for the following indication:

“Substitution therapy in patients dependent on opioids concomitant with medical and psychological treatment and social rehabilitation”.

A comprehensive description of the indications and posology is given in the SPC (see Module 3).

The marketing authorisation in Norway is granted according to Directive 2001/83/EC as amended, Article 10a well-established use application.

Since the application is based on bibliographical data, no reference to other methadone containing products is made. No clinical trials have been performed and no bioequivalence have been carried out. The clinical bibliographical data show that the use of methadone in the applied indication can be regarded as well known. In Norway methadone containing oral solutions had been available for many years before the first solution was granted marketing authorisation as the formulation was manufactured and dispensed by/through pharmacies.

II. QUALITY ASPECTS

II.1 Introduction

Methadone oral solution contains methadone hydrochloride in an aqueous solution. Two strengths are presented. Both strengths are available in brown plastic bottles in a wide range of package sizes. For the 1 mg/ml strength the following presentations are included: 50 ml bottle with 15–50 ml (with increments of 5 ml), 100 ml bottle with 55–100 ml (with increments of 5 ml) and 150 ml bottle with 110–150 ml (with increments of 10 ml). For the 5 mg/ml strength the following presentations are included: 50 ml bottle with 14–50 ml (with increments of 2 ml).

II.2 Drug Substance

Methadone hydrochloride is a synthetic opiate. Methadone hydrochloride is tested according to the specifications in the Ph. Eur., and Certificates of Suitability of the monograph have been presented for both the relevant manufacturers. Stability studies have been performed, and a suitable re-test period has been set. The stability of the drug substance is good.

II.3 Medicinal Product

The product is a colourless solution. With the exception of the flavouring system, well-known excipients are used; these are tested according to Ph. Eur. specifications. Suitable specifications have been presented for the flavouring agents. Methyl parahydroxybenzoate is used as a preservative, and the Ph. Eur. requirements for efficacy of antimicrobial preservation are fulfilled for the product.

The oral solution is manufactured and released at A/S Den norske Eterfabrikk, Oslo, Norway. A manufacturing licence has been presented. The manufacture of the oral solution is simple. The process has been sufficiently described. The tests and limits in the specification for the medicinal product are considered to be appropriate to control the quality of the product.

Based on the submitted stability data a shelf life of 18 months with no special storage conditions is acceptable for the oral solution in the brown plastic (PET) bottles.

III. NON-CLINICAL ASPECTS

The application is submitted as a well-established use application and relies solely on published scientific literature on the non-clinical pharmacology, pharmacokinetic and toxicological properties of methadone hydrochloride.

The use of methadone in the treatment of opioid addiction, both as a detoxification drug and as a part of maintenance treatment program is well established, and a bibliographical application is considered acceptable. The non-clinical pharmacological, pharmacokinetic and toxicological properties of methadone hydrochloride are well known, and have been adequately documented by the submitted bibliography.

IV. CLINICAL ASPECTS

According to *Notice to applicants, vol. 2A*, a bibliographical application with reference to comprehensive references published in the literature, can be used for medical substances having a well established use, recognised efficacy and acceptable level of safety.

The use of methadone in the treatment of opioid addiction, both as a detoxification drug and as a part of maintenance treatment program is well established and accordingly a bibliographical application is considered acceptable.

For the use of methadone in the management of opioid addiction in Norway, methadone can only be prescribed for clients in approved «methadone programmes» where methadone is used as part of a management plan including important elements such as social rehabilitation, management of co-existent diseases (somatic and psychiatric), job training etc. The Ministry of Health and Social Affairs has established guidelines for inclusion (and exclusion) of clients in the programme.

The efficacy and safety of methadone is considered adequately documented for the substitution therapy in patients dependent on opioids concomitant with medical and psychological treatment and social rehabilitation.

V. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Metadon DnE oral solution 1 mg/ml and 5 mg/ml is a well-known medicinal product with an established efficacy and safety profile.

Since the application is based on bibliographical data, no reference to other methadone containing products is made. No clinical trials have been performed and no bioequivalence have been carried out.

Satisfactory chemical pharmaceutical documentation has been provided assuring consistent quality of the product.

The Member States mutually recognised the Norwegian evaluation and the marketing authorisation. There was no discussion in the CMD(h). Agreement between Member States was reached through a written procedure.

Module 6: Update

List of abbreviations

CMD (h)	Co-ordination Group for Mutual Recognition and Decentralised procedures (human)
MA	Marketing Authorisation
SPC	Summary of Product Characteristics