Medicines & Healthcare products Regulatory Agency

MHRA Regulating Medicines and Medical Devices

Public Assessment Report

Decentralised Procedure

Methadone Hydrochloride 5 mg tablets

(Methadone hydrochloride)

Procedure No: UK/H/6569/001/DC

UK Licence Number: PL 39541/0009

Ascot Laboratories Limited

LAY SUMMARY

Methadone Hydrochloride 5 mg tablets

This is a summary of the public assessment report (PAR) for Methadone Hydrochloride 5 mg tablets (PL 39541/0009; UK/H/6569/001/DC). It explains how Methadone Hydrochloride 5 mg tablets were assessed and their authorisation recommended as well as their conditions of use. It is not intended to provide practical advice on how to use Methadone Hydrochloride 5 mg tablets.

For practical information about using Methadone Hydrochloride 5 mg tablets, patients should read the package leaflet or contact their doctor or pharmacist.

What are Methadone Hydrochloride 5 mg tablets and what are they used for?
Methadone Hydrochloride 5 mg tablets are a medicine with 'well established use'. This means that the medicinal use of the active substance methadone hydrochloride is well-established in the European Union (EU) for at least ten years, with recognised efficacy and an acceptable level of safety.

Methadone Hydrochloride 5 mg tablets is used in the treatment of severe pain where morphine may be a reasonable alternative, such as severe cancer pain.

How do Methadone Hydrochloride 5 mg tablets work?
This medicine contains the active ingredient methadone hydrochloride. Methadone hydrochloride is a synthetic opiate (a morphine-like drug). It acts on the Central Nervous (CNS) system and smooth muscles to relieve pain.

How are Methadone Hydrochloride 5 mg tablets used?
The pharmaceutical form of this medicine is a tablet and the route of administration is oral.

The patient must take this medicine exactly as their doctor or pharmacist has told them to. If the patient is unsure they should check with their doctor or pharmacist.

The patient must not drink alcohol whilst taking this medicine as this can cause serious side effects. The patient is advised not to drink grapefruit juice whilst they are being treated with this medicine as it could cause an effect similar to overdose.

Recommended doses:

Adults:
The recommended initial dose is 5-10mg (1 to 2 tablets) every 6 to 8 hours. The dose may be adjusted depending on the level of pain relief the patient needs.

Elderly or ill:
For the elderly or ill, the doctor will only prescribe repeated doses with caution.

Use in children and adolescents
Not suitable.

Please read section 3 of the package leaflet for detailed dosing recommendations, the route of administration, and the duration of treatment.

For further information on how Methadone Hydrochloride 5 mg tablets are used, refer to the package leaflet and Summary of Product Characteristics available on the Medicines and Healthcare products Regulatory Agency (MHRA) website.

This medicine can only be obtained with a prescription.

What benefits of Methadone Hydrochloride 5 mg tablets been shown in studies?
As methadone hydrochloride is a well-known substance and its use in the treatment of severe pain where morphine may be a reasonable alternative, such as severe cancer pain is well-established, the applicant presented data from the scientific literature. The literature provided confirmed the efficacy and safety of the use of methadone hydrochloride in this indication.

In addition, the company (Ascot Laboratories Limited**)** provided a suitable justification to bridge their product to information found in bibliographic sources relating to currently approved methadone hydrochloride-containing products.

What are the possible side effects of Methadone Hydrochloride 5 mg tablets?
Like all medicines, this medicine can cause side effects, although not everybody gets them.

Repeated use of methadone can result in tolerance and addiction.
The patient must stop taking this medicine and see a doctor straight away if they get any of the following side effects:

- Heart problems. The signs of this may include changes in the way the heart beats, such as it is beating faster or missed heart beats, breathing difficulties and dizziness.
- If the patient's breathing become slow and shallow.
- Worsening of the pressure inside the patient's head if the patient already has this condition following an injury to their brain or brain disease.
- Severe itching of the skin with raised lumps.
- Low blood platelet count. Symptoms include bleeding or bruising more easily than normal.

For the full list of restrictions, see the package leaflet.

The most common side effects with Methadone Hydrochloride 5 mg tablets (which may affect up to 1 in 10 people) are:

- fluid retention
- changes in the patient's mood, feeling 'high' or over excited (euphoria)
- seeing or hearing things that are not there (hallucinations)
- low magnesium or potassium levels in the blood
- drowsiness or sleepiness (sedation)
- blurred vision
- small pupils
- vertigo
- fatigue
- constipation
- rash
- sweating
- weight increase

For the full list of all side effects reported with Methadone Hydrochloride 5 mg tablets, see section 4 of the package leaflet available on the MHRA website.

Why were Methadone Hydrochloride 5 mg tablets approved?

The MHRA decided that the benefits of Methadone Hydrochloride 5 mg tablets are greater than its risks and recommended that it was approved for use.

What measures are being taken to ensure the safe and effective use of Methadone Hydrochloride 5 mg tablets?

A risk management plan (RMP) has been developed to ensure that Methadone Hydrochloride 5 mg tablets is used as safely as possible. Based on this plan, safety information has been included in the Summary of Product Characteristics (SmPC) and the package leaflet for Methadone Hydrochloride 5 mg tablets including the appropriate precautions to be followed by healthcare professionals and patients.

Known side effects are continuously monitored. Furthermore, new safety signals reported by patients/healthcare professionals will be monitored/reviewed continuously.

Other information about Methadone Hydrochloride 5 mg tablets

Ireland and the UK agreed to grant a Marketing Authorisation for Methadone Hydrochloride 5 mg tablets on 15 August 2018. Following a subsequent national phase, a Marketing Authorisation was granted in the UK on 11 September 2018.

The full PAR for Methadone Hydrochloride 5 mg tablets follows this summary.

For more information about treatment with Methadone Hydrochloride 5 mg tablets, read the package leaflet, or contact your doctor or pharmacist.

This summary was last updated in November 2018.

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I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Medicines and Healthcare products Regulatory Agency (MHRA) granted Ascot Laboratories Limited, a marketing authorisation for the medicinal product Methadone Hydrochloride 5 mg tablets (PL 39541/0009; UK/H/6569/001/DC). This product is a prescription-only medicine (POM) and is indicated for severe pain where morphine may be a reasonable alternative, such as severe cancer pain.

This application was submitted using the Decentralised Procedure (DCP), with the UK as Reference Member State (RMS) and Ireland (IE) as Concerned Member State (CMS). The application was submitted under Article 10a of Directive 2001/83/EC, as amended, claiming to be an application for a product containing an active substance of well-established use.

Methadone is an opioid analgesic acting in the same manner as morphine, and like morphine, is a highly addictive drug in its own right. It has a less sedative effect than morphine. It acts on the CNS system and smooth muscle. This action is caused by the response of structurally and sterically specific opiate receptor sites in the brain, spinal cord and nervous system.

Methadone is an 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 κ and σ 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 a pA2 value similar to its antagonism of morphine. Like many basic drugs, methadone enters mast cells and releases histamine by a nonimmunological mechanism. It causes a dependence syndrome of the Morphine type.

Bibliographic data on methadone hydrochloride have been submitted to support this application.
No new clinical or non-clinical studies were submitted, which is acceptable given that this is a bibliographic application for a product containing an active substance of well-established use.

The applicant has provided a suitable justification to bridge their product to information found in bibliographic sources relating to currently approved methadone hydrochloride-containing products. All criteria set out in the guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **) for the request of a bio-waiver have been met.

The RMS has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for this product type at all sites responsible for the manufacture, assembly and batch release of this product.

For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

The RMS and CMS considered that the application could be approved at the end of procedure on 15 August 2018. After a subsequent national phase, a licence was granted in the UK on 11 September 2018.

II QUALITY ASPECTS

II.1 Introduction

The finished product is formulated as a tablet containing 5 mg of methadone hydrochloride.
Other ingredients consist of the pharmaceutical excipients:
Lactose monohydrate
Maize starch
Povidone K25
Silica colloidal anhydrous
Talc
Magnesium stearate

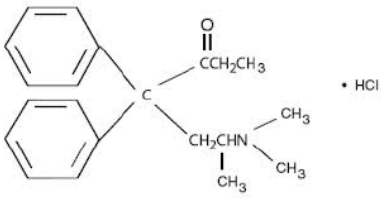
The finished product is presented in in clear, colourless polyvinyl chloride/polyvinylidene chloride/aluminium (PVC/PVDC/Al) blisters in a carton box with leaflet containing 28, 30 or 50 tablets. Not all pack sizes may be marketed.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary packaging complies with the current European regulations concerning materials in contact with food.

II.2 Drug Substance

INN:	Methadone hydrochloride
Chemical name:	(6*RS*)-6-(Dimethylamino)-4,4-diphenylheptan-3-one hydrochloride

Structure:



Molecular formula:	$C_{21}H_{28}ClNO$
Molecular weight:	345.9 g/mol
Description:	White, or almost white, crystalline powder
Solubility:	Soluble in water, freely soluble in ethanol (96 per cent).

Methadone hydrochloride is the subject of a European Pharmacopoeia monograph.

All aspects of the manufacture and control of the active substance of methadone hydrochloride are covered by the European Directorate for the Quality of Medicines and Healthcare (EDQM) Certificates of Suitability.

II.3. Medicinal Product

Pharmaceutical Development

The objective of the development programme was to formulate safe, efficacious, tablets containing 5 mg methadone hydrochloride per tablet. A satisfactory account of the pharmaceutical development has been provided.

Comparative impurity profiles based upon the comparison of qualitative compositions of products containing methadone. Metadon DAK tablets (Nycomed, Denmark) were chosen as representative with

respect to physico-chemical characteristics and biological properties of marketed products; and was used in pre-formulation studies to assess the target in vitro dissolution profile for the product developed by the applicant.

From a quality point of view all criteria set out in the guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **) for the request of a bio-waiver have been met.

All excipients comply with their respective European Pharmacopeia monographs. Suitable batch analysis data have been provided for each excipient.

None of the excipients used contain material of animal or human origin. Confirmation has been given that the magnesium stearate used in the tablets is of vegetable origin.

This product does not contain or consist of genetically modified organisms (GMO).

Manufacture of the product
Satisfactory batch formulae have been provided for the manufacture of the product, together with an appropriate account of the manufacturing process. Process validation data on pilot scale batches have been provided. The results are satisfactory.

Finished Product Specification
The finished product specification proposed is acceptable. Test methods have been described that have been adequately validated. Batch data complying with the release specification have been provided. Certificates of Analysis have been provided for all working standards used.

Stability of the Product
Finished product stability studies were performed in accordance with current guidelines on batches of the finished product in the packaging proposed for marketing. The data from these studies support a shelf-life of 5 years with no special storage conditions.

Suitable post approval stability commitments to continue stability testing on batches of finished product have been provided.

II.4 Discussion on chemical, pharmaceutical and biological aspects
There are no objections to the approval of this application from a pharmaceutical viewpoint.

III NON-CLINICAL ASPECTS
III.1 Introduction
The pharmacological, pharmacokinetic and toxicological properties of methadone hydrochloride have been well characterised. New non-clinical studies are not required and the applicant has not conducted any. A literature review is, therefore, appropriate. The applicant has provided an adequate discussion of the literature on the pharmacology, pharmacokinetics and toxicity of methadone hydrochloride.

The primary and secondary pharmacology of methadone hydrochloride has been reviewed adequately in the applicant's non-clinical overview. As the drug substance has been in use for many years, further discussion of non-clinical data is not warranted

The applicant's non-clinical expert report has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the relevant non-clinical pharmacology, pharmacokinetics and toxicology.

III.2 Pharmacology

The pharmacology of the active substance, methadone hydrochloride is adequately discussed in the applicant's non-clinical overview and is briefly summarised below.

Methadone is a synthetic μ-opioid receptor agonist; in addition to its opioid receptor activity, it is also an antagonist of the N-methyl-D-aspartate (NMDA) receptor. Methadone is a racemic mixture of 2 enantiomers; the l- (R-; -) form is more potent, with a 10-fold higher affinity for opioid receptors (which accounts for virtually all of its analgesic effect), while d- (S-; +) methadone is the NMDA antagonist.

It was demonstrated in rat brain homogenate *in vitro*, that methadone has a high affinity to the μ-, showing considerably less or no affinity to the other δ- and κ-opioid receptors in rats.
The two enantiomers or methadone show different affinity to the μ-opioid receptor. In radioligand competition assays an ED_{50} of 0.02 and 0.2 μM or a Ki of 0.945 and 19.7 nM for the l- and the d-methadone was determined in rats and Ki of 3.4 and 105 nM for guinea pig μ-opioid receptor expressed in CHO cells.

l-methadone was 16.5-fold more potent, than *d*-methadone (EC_{50}= 37±3.8 nM and 609±73.4 nM, respectively) activating μ-opioid receptors when measured by the increase of the potassium conductance mediated by G-protein-coupled, inwardly rectifying, potassium (KIR3) channels with intracellular and whole-cell recording from locus coeruleus neurons in rat brain slices. Both enantiomers were full μ-opioid agonist, if assayed by the intracellular, current-clamp method, but only partial μ-opioid agonists if assayed by the whole cell patch clamp method.

Methadone exerts its effect at very low levels of opioid receptor occupancy (<10%) established by ^{11}C-diprenorphine PET.

Methadone (racemic and separate enantiomers) was shown to be an effective, non-competitive inhibitor of NMDA receptor with a K_i value of 0.85 μM in the rat cortical membrane, 8.3 μM in the rat forebrain and 2.5 μM in the rat spinal cord. *d*-methadone had somewhat higher affinity (2-fold) compared to *l*-methadone in the forebrain but not in the spinal cord. Methadone decreased the depolarizing effect of NMDA in a use-dependent manner to 4±3% and 23±4%, in the rat cortical and spinal preparations, respectively.

In vivo spike-frequency analysis, showed that in intact rats, pre-treated with naloxone, methadone reduced the NMDA induced neuronal hyperactivity; while in rats with sciatic nerve blockade, a model for neuropathic pain, methadone inhibited the neuronal spontaneous and noxious evoked hyperactivities, which was reversible by naloxone only up to 60%.

Methadone was found to be the most effective amongst different substitutive opiates in reducing morphine withdrawal symptoms in rats. In monkeys, methadone was found to be more effective than buprenorphine, in decreasing heroin self-administration, when withdrawal-associated increases in opiate reinforcement was assayed.

In a rat model of polydrug abuse daily administration of a relatively high dose of methadone (30 mg/kg, subcutaneous (SC) by osmotic minipump) significantly decreased both heroin and cocaine self-administration assessed during an extinction period and after priming injections of heroin and cocaine. In the same experiment methadone failed to reduce the reinstatement of drug seeking induced by foot-shock stress.

Methadone maintenance of heroin dependence produced a greater extent of μ-opioid receptor desensitization compared with heroin self-administration alone in different rat brain regions, which might play a role in the differing rate of tolerance development against these two agents.

Morphine self-administration was markedly reduced initially but returned to normal levels within 2 weeks of methadone administration in dogs in a model, where morphine was freely available during the maintenance period. Following the methadone maintenance period, morphine self-administration was increased over the premaintenance period for 2 weeks, while no marked changes were seen in self-administered morphine dose in dogs kept on morphine maintenance.

Methadone (1.43.-11.86 mg/kg/day) failed to suppress opiate self-administration in four of five monkeys across a dose range equivalent to 100 to 800 mg/day in human, where intravenous (IV) drug self-administration (heroin 0.01 or 0.02 mg/kg/injection or hydromorphone 0.02 mg/kg/injection) was maintained on a schedule of reinforcement.

In normal and μ1-receptor deficient mice SC methadone administration induced a naloxone reversible analgesia, indicating a predominant involvement of the μ2-receptor in this action. Methadone antinociception seems to be significantly dependent on an action of the drug at peripheral sites, since its analgesic potency is reduced if administered spinally or intracerebroventricularly.

In rats the degree of hyperalgesia was greater with *l*-methadone compared with *d,l*-methadone, while *d*-methadone (NMDA receptor antagonist) did not produce hyperalgesia. Furthermore, if *d*- or *l*-methadone and morphine were administered together, d-methadone blocked morphine hyperalgesia and enhanced antinociception, which might be the result of antagonistic activity of *d*-methadone at the NMDA receptor. In other studies, the NMDA receptor antagonism was not playing a role in morphine analgesia, since the developed antinociception after the drug treatment could be fully blocked by different μ-opiate antagonists (e.g. naloxone, nalbuphine).

Administered chronically to rats, *d*-methadone dose-dependently blocked tolerance development against analgesia to the *l*-isomer.

In rat models of peripheral and central neuropathic pain methadone (0.5–5 mg/kg, SC or intraperitoneal (IP) administration) dose-dependently attenuated mechanical- and cold- or heat allodynia. The most potent analgesic was shown to be *l*-methadone, and the antiallodynic effect could be blocked completely by opiate antagonist naloxone.

IP administration of methadone in the dose range of 1.25-20 mg/kg caused arousal in treated animals, characterised by increased locomotor activity and desynchronized tracings on the EEG.

NMDA-antagonist agents are used in therapeutic practice with aim of neuroprotection in cases when neuronal loss is related a glutamate-induced excitotoxicity (i.e. ischemia), or when excess glutamate is not the primary problem but compromised neurons become sensitized to excitotoxic damage (i.e. Parkinson's disease or Huntington chorea). Furthermore, recent research investigating in more depth pharmacological consequences of the NMDA-antagonism by methadone have shown a paradoxical, glutamate-like excitotoxic effect of methadone in a neuroblastoma cell line in vitro. This observation might stand at the basis to explain the mechanism of CNS degenerative side effects associated with methadone treatment.

In rats and dogs, methadone causes bradycardic and hypotension, mediated through μ-opioid receptors, these effects being antagonized by the concomitant administration of naloxone.

d-methadone blocks the hERG current 3.5-fold more potently than *l*-methadone *in vitro*. In an isolated, perfused rabbit heart model, QTc prolongation methadone caused a dose dependent QTc prolongation apparent at concentrations as low as 1 to 3 μM, and significant at 10 and 30 μM. In rats (9-30 mg/kg,

cumulative IV doses), methadone caused a significant and dose-dependent prolongation of the QTc interval.

Rats and dogs, exposed to methadone (2.5-7.5 mg/kg IP, 0.3-5.6 mg/kg intramuscularly (IM), or; 2 mg/kg SC) exhibited a dose-dependent respiratory depression that involved hypoxemia, hypercapnia, acidosis, increased inspiratory and expiratory time and pulmonary vascular resistance. In monkeys, methadone reduced the ventilatory stimulant effect of increased carbon dioxide presence in the air. Chronic methadone treatment (2.5-7.5 mg/kg/day, 14 days, IP) conferred a substantial tolerance to the respiratory depressant action of methadone.

Cathecol-O-methyltransferase inhibitors decreased methadone LD50 to 14 mg/kg from 24 mg/kg or 26 mg/kg in male and female rats, respectively.

Clomipramine produced a proportion-dependent enhancement of the antinociceptive effect of methadone.

High dose flunitrazepam augments lethality two-fold in methadone-treated rats and six-fold in buprenorphine-treated rats. Flunitrazepam administration appeared to have no significant effect on morphine lethality.

III.3 Pharmacokinetics

The pharmacokinetics of the active substance, methadone hydrochloride is adequately discussed in the applicant's non-clinical overview and are briefly summarised below.

The absorption of methadone after ingestion of oral doses in rats is rapid, after 20 minutes more than 60% of the drug disappears from the stomach and small intestine. Intestinal absorption was found to be directly proportional to the dose administered, however, absorption from the stomach was markedly slower (only around 5.5% after 20 min), which could be increased by alkalinisation of stomach contents (up to 29.2%). Gastric emptying of methadone appears to be the rate-limiting step in the overall gastrointestinal absorption in rats.

The absolute oral bioavailability of methadone in dogs, which is in contrast to humans, is low varying between 0-29%. Methadone is a subject of an extensive first-pass metabolism in both rats and dogs, which accounts for the disappearance of 70-100% of the drug and gives an explanation to the low bioavailability in these species.

Methadone pharmacokinetic parameters did not show dose proportionality in the tested animal species, since after administration of a single high dose, or repeated doses, methadone might induce or inhibit its own metabolism which, in return results in altered plasma concentrations or half-lives.

A lower analgesic efficacy in female rats was accompanied by higher plasma concentration and lower central clearance values when compared to the males.

Pharmacokinetic parameters of the two distinct methadone enantiomers were similar in dogs if administered separately, however, after administration of the racemate, the clearance of the *d*-enantiomer increased significantly (compared to both the *l*-enantiomer and to its own) leading to a decreased total disposition.

After a single dose methadone persisted for a longer period of time in the organs of elimination (liver, kidney, lung) as well as in spleen and brain (due to a long-lasting brain protein conjugate in case of *l*-enantiomer).

Hepatic extraction of methadone was shown to be excessive in an *ex vivo* perfused rat liver model, in 10 min more than 65% of the perfused drug disappeared from the perfusate.

After a single dose, methadone accumulated in the pigmented rat eye and showed persistence measured up to 6 days.

After repeated methadone administration a smaller fraction of the total amount of drug could be recovered in the internal organs (liver, lung, skin, kidney), in the brain and in the whole animal carcass compared to single-dose administration. This trend was found to be reversed in the skin and intestines (together with the content of the intestines), indicating a deposit formation in the skin and an increased excretion into the faeces after chronic methadone administration.

Data for the volume of distribution of methadone after a single IV injection are available for rats, 1.5 7.35±0.95 and 7.81±1.65 l/kg after 0.9 and 1.5 mg/kg dose, rabbits, 12.6 l/kg after 40 mg/kg and dogs, 9.2±3.3 after 0.4 mg/kg.

Protein binding was high in rats and guinea pigs, 79-81% and 91.9% respectively. In guinea pigs the "physiological" binding rate was demonstrated to stay unchanged during pregnancy and lactation (89.9% and 88.6%, respectively).

Methadone was shown to cross the placenta in mice, rats, guinea pigs and monkeys and was found in lower concentrations in the foetal plasma and tissues than that found in the dam. An exception was the brain, which showed a higher methadone level in foetuses in mice, rats and guinea pigs. In rats the difference between the brain methadone level of the dam and pups proved to disappear after repeated administration.

The metabolite pattern was almost identical in rats and dogs and were formed according to the following routes: derivatives arising out of mono-N-demethylation and cyclization: 2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidin (EDDP, the main metabolite) and 2-ethyl-5-methyl-3,3-diphenylpyrroline (EMDP); N-oxidation; p-aromatic hydroxylation; glucuronide or sulfate conjugation at the p-hydroxy position and at the secondary alcohol group; reduction of hindered keto group to a secondary alcohol (resulting in methadol) which is only a minor route but it can prevent cyclization of the p-hydroxy N-mono-demethylated methadone. Further minor metabolites were identified as p-hydroxylated pyrrolidine and pyrroline derivatives and unidentified phenolic tertiary amine metabolites. Most of these metabolites were described in humans as well. Dimethylamino-2,2-diphenylpentanoic acid was also reported from human urine and was hypothesized to be a biliary metabolite in rats as well. Metabolites of methadone were reported to be inactive.

Studies conducted on enzyme induction or inhibition capacity of methadone indicate interspecies differences. Methadone stimulates the hepatic mixed function oxidase system (methadone and/or aminopyrine N-demethylase, aniline and/or pentobarbital hydroxylase) in mice it depresses this microsomal drug-metabolizing system in rats, guinea pigs and monkeys.

The relative importance of urinary or biliary elimination differs across species, in rats only ca. 1.5-7% of total radioactivity having been detected in urine while male dogs seem to excrete methadone by this route in proportion of 25-32%. Female dogs, in the meantime excreted only 9% of methadone metabolites into the urine.

Biliary excretion accounted for up to 85% in rats and 54% in dogs. Clearance of methadone from plasma is rapid, rates of 56.2-77 ml/min/kg for male, a higher value of 102 ml/min/kg for female rats and 25.14-

27.9 ml/min/kg having been reported for dogs. In these species, the terminal elimination half-life was 1.46-1.50 h and 1.92 h in rats and dogs, respectively after administration of single IV doses.

For rats an apparent entero-hepatic recirculation was also noted to be only around 1.5% after 3 hours. Methadone is excreted into the milk and was detected in suckling guinea pig pups, although in a lower concentration as in the dams.

III.4 Toxicology

The toxicology properties of methadone hydrochloride are discussed in detail in the applicant's non-clinical overview. The summaries of these findings are presented below:

LD_{50} of methadone was determined after oral, SC, IP and IV administration to be 100-150, 54, 24 and 22 mg/kg, respectively in male rats. One study reported the half maximal lethal dose in female rats to be 26 mg/kg, after IP administration.

Administration of methadone caused sedation in rats (1-20 mg/kg IP) and dogs (1mg/kg IV) with a concomitant arousal period. The time of onset of sedation showed an administration site and dose dependent duration.

In rats, dose- related mydriasis occurred after SC or IV administration, was stereospecific and independent of behavioural responses. Chronic methadone decreased testosterone, LH, TSH, T4-T3 and cortisone in male rats.

In mice and rats after oral, SC or IV administration (3-100 mg/kg/day), tolerance to methadone lethality and analgesic effect was observed. A cross-tolerance to morphine analgesia, but interestingly not to morphine lethality was also reported.

Gastrointestinal transit time was prolonged in rats and guinea pigs. It appeared that in guinea pigs, μ-, as well as κ-opioid receptors were participating in this action of methadone. In rats, methadone appeared to inhibit vagal stimulation of digestive (pancreatic, gastric) secretions.

Rats and dogs exposed to methadone exhibited respiratory depression that involved hypoxemia, hypercapnia, acidosis, increased inspiratory and expiratory time and pulmonary vascular resistance. These effects were dose-dependent and correlated well with plasma methadone levels after IV administration.

In dogs, IV anaesthetic doses of methadone (0.5, 1.0, 1.8, 3.3 and 5.3 mg/kg) produced only modest cardiovascular changes, including decreased heart rate, cardiac output and aortic blood pressure and a slightly increased pulmonary vascular resistance.

Chronic methadone treatment in dogs (2.5-7.5 mg/kg/day, 14 days, IP) conferred a substantial tolerance to the respiratory depressant action of methadone, which was observed after a single dose.

In monkeys, methadone reduced the ventilatory stimulant effect of increased carbon dioxide presence in the air. It was established that methadone-induced hypoxemia is caused by μ-opioid receptor and modulated by κ-opioid receptors. Additionally, methadone-induced increase in expiratory time is caused by μ1- and δ-opioid receptors while increase in inspiratory time is caused by μ1- and μ2-opioid receptors. A decrease in dehydroepiandrosterone sulphate in pregnant monkeys was observed following chronic methadone dosing.

A sudden and potentially lethal toxic reaction to a previously well-tolerated maintenance

dose of methadone after 3-28 weeks was reported in stump-tailed monkeys. The reaction was characterized by gross behavioural and respiratory depression and a marked attenuation of both early and late components of the visual evoked response with an increase in most latencies along with increased methadone plasma concentrations.

However, an increased unspecific IgG level, reduced phagocytosis, killing and superoxide anion production of isolated polymorphonuclear cells and decreased NK cell activity was apparent after 4 day SC (5-20 mg/kg/day incrementally increased) or 6 weeks oral drug intake (0.2 or 0.4 mg/g food).

Methadone causes a higher degree of μ-opioid receptor desensitization in the rat brain, than low or high doses of heroin. The reporting authors deduced that both the enhancement of the methadone N-demethylase activity upon chronic treatment and cellular adaptive metabolism (receptor endocytosis and recycling) might account for the decreased activity of methadone after the administration of multiple doses.

Methadone was found to be non-genotoxic under *in vitro* conditions, or *in vivo* in *Drosophila melanogaster* and rat bone marrow cells (2.4-72.0 mg/kg, SC single or for 6 days), however there were weak positive results in the microbial suspension test conducted with E. coli WP2uvrA strain, ad-3 forward mutation test in *Neurospora crassa* in the absence of the activating S9 mix. In mice 1-6 mg/kg/day IP for 3 days resulted in several numeral or structural chromosomal aberrations of the spermatocytes, so that results can be interpreted as inconclusive in these models.

In vitro conditions in several mammalian cancer cell lines and *in vivo* in a nude mouse xenograft model, methadone was found to decrease cell growth in various cancer cell lines. *In vivo* in mice and rats, methadone (15-60 mg/kg/day, 20-60 mg/kg/day, orally respectively, for 2 years) did not influence the appearance of neoplastic lesions.

A blockade in ovulation was observed in female rats (6-15 mg/kg, 3 times, proestrus). Also, methadone dose-dependently (1-16 mg/kg, IP) blocked the sexual activity of male hamsters, while their ambulatory activity was unaffected.

In mice, an increase in the rate of preimplantation deaths, decreased fertility, detrimental effect on the developing nervous system was seen at doses of 4-6 mg/kg IP or 25-35 mg/kg SC. However, in rats, no teratogenic or embryotoxic outcome of methadone (2-20 mg/kg/day SC or 20-40 mg/kg/day oral) treatment was noted, except a slight decrease in the fertility rate (~10%).

Methadone was found to have some detrimental effect on mouse foetuses, but no effect was found in rats or rabbits. Administration of methadone (5-28 mg/kg/day, during gestation, SC decreased ossification of the digits, sternum, and skull of the offspring in mice. Administration of methadone (20-40 mg/kg/day, orally during the same period of gestation, day 6-18) resulted in no external, visceral or skeletal malformations in the developing foetuses.

Methadone exposure during gestation results in pups, weighing less than control animals (15-25% deficit) in mice (40 mg/kg/day, SC 10 days), rats (2.86 mg/kg/day, orally) and monkeys as well.

Some neurological and behavioural differences were also observed in rat pups born to methadone treated dams or does, namely decreased imipramine binding site paralleled with decreased serotonin uptake capacity in rat brain (60-80 mg/kg/day orally during the whole gestation), increased anxiety, especially if combined with lactational methadone exposure (2.86 mg/kg/day, orally, during gestation and lactation) and altered open field activity, cage activity, passive avoidance latencies, shuttle box avoidances, and rotarod

latencies (males, 5 mg/kg/day SC for 4 days, prior mating).

Prenatally methadone exposed rat pups (7 mg/kg/day, SC 18 days) developed a tolerance to morphine analgesia more quickly, than the control animals did. Moreover, rat infants exposed to methadone prenatally and postnatally via the dam's milk (9-14 mg/kg/day, SC) experienced opiate withdrawal syndromes, indicating that dependence can develop in the newborn during maternal drug exposure.

Impurities
The specifications for the finished product comply with the European Pharmacopoeia for tablets and the ICH Q6A guideline "Note for guidance specifications: test procedures and acceptance criteria for new drug substances and new drug products: chemical substances (CPMP/ICH/367/96).

None of the potential impurities specified for methadone hydrochloride drug substance and no unspecified degradation product was detected above the disregard limit (0.05%).

Impurities of the drug substance do not need to be monitored or specified in the drug product unless they are also degradants, which the stability data do not indicate, therefore impurities A-E are not included in the drug product specifications.

III.5 Ecotoxicity/environmental risk assessment (ERA)
Since Methadone hydrochloride 5 mg tablets are intended for generic substitution, this will not lead to an increase of the environment exposure. An environmental risk assessment is therefore not deemed necessary**.**

III.6 Discussion on the non-clinical aspects
There are no objections to the approval of this application from a non-clinical viewpoint.

IV CLINICAL ASPECTS
IV.1 Introduction
The pharmacodynamic, pharmacokinetic, clinical efficacy and safety properties of methadone hydrochloride are well known. A comprehensive review of the published literature has been provided by the applicant. The clinical overview has been written by an appropriately qualified person and is considered acceptable.

The SmPC and all product literature have been updated to be in line with comparative approved methadone products.

A bibliographic application submitted under Article 10a of Directive 2001/83/EC, as amended, claiming to be an application for a product containing an active substance of well-established use is treated as a 'full dossier' and therefore the data presented should be an appropriate and robust substitute for the clinical data from an originator or new drug application. These data must be satisfactorily bridged to the proposed product.

The clinical overview and response documents provided by the applicant support a biowaiver so that a bioequivalence study is not considered necessary.

A biowaiver is considered appropriate for this application in line with the note for guidance on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/Corr**) and is adequately supported by the clinical overview and associated data provided and thus a bioequivalence study is not considered essential for this application. The applicant also provided a bridging of the data in the clinical overview to the proposed product and this was considered acceptable without the need for a bioequivalence study to bridge to the relevant literature on methadone.

The overview shows that methadone has been utilised as far back as 1952 with data on availability in the UK from 1990 and 14000 publications from which 160 have now been utilised. The overview contains sufficient evidence to support this application for a product containing an active substance of well-established use of Methadone Hydrochloride 5 mg tablets for its use as an analgesic for more than 10 years.

IV.2 Pharmacokinetics

No new pharmacokinetic data were submitted and none were required for an application of this type.

The pharmacokinetic properties of methadone are discussed in detail in the applicant's clinical overview. A summary of these findings is presented below.

Absorption

Methadone is rapidly absorbed following oral administration but undergoes considerable first-pass metabolism. The bioavailability is above 80 %. Steady state concentrations are reached within 5-7 days.

Distribution

Distribution volume: 5 L/kg. Protein binding: up to 90 %, but with great individual differences. Methadone binds mainly to alpha1-glycoprotein acid, but also to albumin and other plasma and tissue proteins. Plasma: the full blood ratio is around 1:3. It is distributed to tissue with higher concentrations in the liver, lungs and kidneys than in the blood.

Metabolism

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

Pharmacokinetic interactions

P-glycoprotein inhibitors: Methadone is a substrate of p-glycoprotein; all medicinal products that inhibit P-glycoprotein (e.g. qunidine, verapamil, ciclosporin), may therefore raise the serum concentration of methadone. The pharmacodynamic effect of methadone may also increase because of increased blood brain barrier passage.

CYP3A4-enzyme inducers: Methadone is a substrate of CYP3A4 (see section 5.2). By induction of CYP3A4, clearance of methadone will increase, and the plasma levels decrease. Inducers of this enzyme (barbiturates, carbamazepine, phenytoin, nevirapine, rifampicin, efavirenz, amprenavir, spironolactone, dexamethasone, Hypericum perforatum - St John's Wort), may induce hepatic metabolism. For instance, after three weeks treatment with 600 mg efavirenz daily, the mean maximal plasma concentration and AUC decreased by 48 % and 57 % respectively, in patients treated with methadone (35-100 mg daily). The consequences of enzyme induction are more marked if the inducer is administered after treatment with methadone has begun. Abstinence symptoms have been reported following such interactions and hence, it may be necessary to increase the methadone dose. If treatment with a CYP3A4 inducer is interrupted, the methadone dose should be reduced.

CYP3A4-enzyme inhibitors: Methadone is a substrate of CYP3A4 (see section 5.2). By inhibition of CYP3A4 clearance of methadone is lowered. Concomitant administration of CYP3A4 inhibitors (e.g. cannabinoids, clarithromycin, delavirdine, erythromycin, fluconazole, grapefruit juice, itraconazole, ketoconazole, fluoxetine, fluvoxamine, nefazodone and telithromycin) may result in increased plasma concentrations of methadone. A 40-100 % increase of the quote between the serum levels and the methadone dose has been shown with concomitant fluvoxamine treatment. If these medicinal products

are prescribed to patients on methadone maintenance treatment, one should be aware of the risk of overdose.

Products that affect the acidity of the urine: Methadone is a weak base. Acidifiers of the urine (such as ammonium chloride and ascorbic acid) may increase the renal clearance of methadone. Patients that are treated with methadone are recommended to avoid products containing ammonium chloride.

Concomitant HIV infection treatment: Some protease inhibitors (amprenavir, nelfinavir, lopinavir/ritonavir and ritonavir/saquinavir) seem to decrease the serum levels of methadone. When ritonavir is administered alone, a twofold AUC of methadone has been observed. The plasma levels of zidovudine (a nucleoside analogue) increase with methadone use after both oral and intravenous administration of zidovudine. This is more noticeable after oral than after intravenous use of zidovudine. These observations are likely caused by inhibition of zidovudine glucuronidation, and therefore, decreased clearance of zidovudine. During treatment with methadone, patients must be carefully monitored for signs of toxicity caused by zidovudine, why it may be necessary to reduce the dose of zidovudine. Because of mutual interactions between zidovudine and methadone (zidovudine is a CYP3A4 inducer), typical opioid abstinence symptoms may develop during concomitant use (headache, myalgia, fatigue and irritability).

Didanosine and stavudine: Methadone delays the absorption and increases the first pass metabolism of stavudine and didanosine which results in a decreased bioavailability of stavudine and didanosine. Methadone may double the serum levels of desipramine.

Elimination
Elimination half-life: single dose: 10-25 hours. Repeated doses: 13-55hours. Plasma clearance is around 2 ml/min/kg. About 20-60 % of the dose is eliminated in urine over 96 hours (about 33 % in unmodified form, about 43 % as EDDP and about 5-10 % as EMDP). The ratio between EDDP and unmodified methadone is usually much higher in urine in patients receiving methadone treatment compared to normal overdoses. Elimination of unmodified methadone in urine is pH dependent and increases with increasing acidity of the urine. About 30 % of the dose is eliminated in faeces, but this percentage will normally be reduced at higher doses. About 75 % of overall elimination is unconjugated.

Special populations
There are no significant differences in the pharmacokinetics between men and women. The clearance of methadone is decreased only to some extent in elderly (>65 years). Because of increased exposure, caution is advised in the treatment of patients with renal and hepatic impairment.

IV.3 Pharmacodynamics

No new pharmacodynamic data were submitted and none were required for this bibliographic application. The pharmacodynamic properties of methadone are discussed in detail in the applicant's clinical overview. A summary of these findings is presented below.

Mechanism of action
Methadone is a synthetic diphenylheptane derivative, being primarily an opioid agonist with similar pharmacological effects to that of morphine. Methadone is an opioid analgesic: like morphine it is a highly addictive drug in its own right but with a less sedative effect than morphine. It acts on the CNS system and smooth muscle. This action is caused by the response of structurally and sterically specific opiate receptor sites in the brain, spinal cord and nervous system.

Methadone's opioid agonist actions occur 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 κ and σ 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 automotor nerve and perhaps on opioid receptors in the pupillary muscles causes pupillary constriction. All these effects are reversible by naloxone with a pA2 value similar to its antagonism of morphine. Like many basic drugs, methadone enters mast cells and releases histamine by a nonimmunological mechanism. It causes a dependence syndrome of the morphine type.

Pharmacodynamic interactions
Opioid antagonists: Naloxone and Naltrexone counteracts the effects of methadone and induces abstinence.

CNS depressants: Medicinal products with a sedative effect on the central nervous system may result in increased respiratory depression, hypotension, strong sedation or coma, therefore it may be necessary to reduce the dose of one or both of the medicinal products. With methadone treatment, the slowly eliminated substance methadone, give rise to a slow tolerance development and every dose increase may after 1-2 weeks give rise to symptoms of respiratory depression. The dose adjustments must therefore be made with caution and the dose increased gradually with careful observation.

Peristalsis inhibition: Concomitant use of methadone and peristalsis inhibiting medicinal products (loperamide and diphenoxylate) may result in severe obstipation and increase the CNS depressant effects. Opioid analgesics, in combination with antimuscarinics, may result in severe obstipation or paralytic ileus, especially in longterm use.

QT-prolongation: Methadone should not be combined with medicinal products that may prolong the QT interval such as antiarrhythmics (sotalol, amiodarone, and flecainide), antipsychotics (thioridazine, haloperidol, sertindol, and phenothiazines), antidepressants (paroxetine, sertraline) or antibiotics (erythromycin, clarithromycin).

MAO-inhibitors: Concomitant administration of MAO-inhibitors may result in reinforced CNS-inhibition, serious hypotonia and or apnoea. Methadone should not be combined with MAO-inhibitors and two weeks after such treatment (see section4.3).

Opioid analgesics delay gastric emptying, thereby invalidating test results. Delivery of technetium Tc 99m disofenin to the small bowel may be prevented and plasma amylase and plasma lipase activity may increase because opioid analgesics may cause constriction of the sphincter of Oddi and increased biliary tract pressure; these actions result in delayed visualization and thus resemble obstruction of the common bile duct.

The diagnostic utility of determinations of these enzymes may be compromised for up to 24 hours after the medication has been given. Cerebrospinal fluid pressure (CSF) may be increased; effect is secondary to respiratory depression –induced carbon dioxide retention.

Ciprofloxacin may increase levels of methadone by inhibiting its metabolism. With anti-arrhythmics there may be a delayed absorption of mexiletine.

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

IV.4 Clinical efficacy

No new efficacy data were submitted and none were required for an application of this type. The applicant discussed the therapeutic indication (Severe pain where morphine may be a reasonable alternative, such as severe cancer pain) in the clinical overview and a summary based upon the literature review is presented below.

Methadone is an effective agent in the management of severe pain as well as in the treatment of opioid dependent patients undergoing withdrawal of illicit opioid use. These therapeutic benefits are known to primarily arise from the agonism on μ-opioid receptors hence methadone has similar pharmacodynamic effects to that of morphine. Methadone is a racemic mixture of *l*- and *d*- isomer out of which the former has considerably higher pharmacological activity.

Recent therapeutic guidelines as well as reviews on the published trials on the efficacy of opioid analgesics have endorsed the vast evidence for methadone, as a potent and convenient analgesic. In particular a number of randomised studies have endorsed this analgesic efficacy of methadone in patients suffering from cancer and non-cancer related severe pain.

Cancer related pain

Several randomised studies comparing methadone and morphine in patients suffering from severe cancer-related pain were selected for review, all showing similar pain response rates, although required dose increases for morphine were generally greater than for methadone.

Non-cancer related pain

Despite an apparently large group of publications addressing the efficacy of methadone hydrochloride as an analgesic in non-cancer pain, relatively few studies were considered to have an adequately controlled design others having had basic design shortages (i.e. no comparator group, had no pain outcome, enrolled fewer than 10 participants, did not presented methadone data separately or were case studies).

In a randomized, double-blind, placebo-controlled cross-over trial, aiming to investigate the efficacy of low dose [5mg bd] and high dose [10mg bd] methadone in patients with non-malignant chronic neuropathic pain, there were statistically significant improvements in all three pain outcomes in the "high-dose" phase of the trial on days when 20 mg of methadone was received compared with placebo; analgesic effects were also seen with the lower dose of methadone. In a comparative cross-over study with morphine, again in patients with chronic neuropathic pain, reduction in pain was found to be greater with morphine than methadone. Daily dose ranges were reported as somewhat higher for morphine compared with methadone.

General dosing recommendations

Studies retrieved from the public domain as being relevant from the efficacy of methadone in severe pain included non-opioid naïve patients. Daily doses in these studies typically ranged from 5 mg to 80 mg.

Clinical guidelines suggest that in general, methadone should be initiated with doses as low as 5-10 mg 1-3 times daily in opioid naïve patients, whereas for individuals who had been previously treated with strong opioids the starting dose could be 5-20 mg b.i.d. or t.i.d.

Based on the individual response to methadone therapy, dose can be slowly increased with 5 mg steps throughout the several weeks of titration period.

Usually, the maximum dose should not exceed 100 mg, however, patients who developed strong tolerance to opioids may require higher doses. Since the majority of the unwanted side effects are dose-dependent, higher methadone doses should be administered under strict medical supervision.

High-dose methadone analgesia
In patients suffering from severe pain in which either iatrogenic or recreational opioid-tolerance has developed, the benefit of methadone analgesia can be reached only by administering the drug in a high dose range.

However this is beyond the scope of the granted posology for this product and is not reviewed in detail in this clinical overview.

Treatment of opioid dependence
Methadone is a standard pharmacological intervention for opioid addicts by substituting for long acting opioid agonists administered under medical supervision. Again, this is outside the scope of the current granted indications for this product.

IV.5 Clinical safety

No new safety data were submitted, and none are required for this bibliographic application. The clinical safety of methadone 5mg tablets are discussed in detail in the applicant's clinical overview. The summaries of these findings are presented below.

The safety profile of methadone, as a whole, is well established. The most common adverse reactions to methadone are constipation, vomiting and dizziness; though serious adverse reactions such as QTc prolongation or *torsades de pointes* are also known. Another serious side effect of methadone is respiratory depression.

The pharmacological basis for most of the adverse reactions to methadone resides in its agonist binding to the μ-receptors being responsible for the respiratory depression, euphoria, sedation, decreased gastrointestinal motility and dependence.

Much of these data have been derived from the higher doses of methadone associated with therapy as an opioid substitute in addicts and will be less marked with the lower dosages associated with this analgesic indication.

IV.6 Risk Management Plan (RMP) and Pharmacovigilance System

The applicant has submitted a risk management plan (RMP), in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to colchicine.

A summary of safety concerns and planned risk minimisation activities, as approved in the RMP, are listed below:
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Summary of safety concerns	
Important identified risks	QT interval prolongation (including Torsade de Pointes) Abuse/misuse/dependence/diversion Overdose Interaction with MAO inhibitors Interaction with alcohol Interaction with CYP3A4 inhibitors Renal and liver failure Intoxication in children
Important potential risks	Use in elderly
Missing information	Use in pregnancy Use in children

Routine pharmacovigilance and routine risk minimisation are proposed for all safety concerns.

IV.7 Discussion on the clinical aspects

The grant of a Marketing Authorisation is recommended for this application from a clinical viewpoint.

V User consultation

The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The language used for the purpose of user testing the PIL was English.

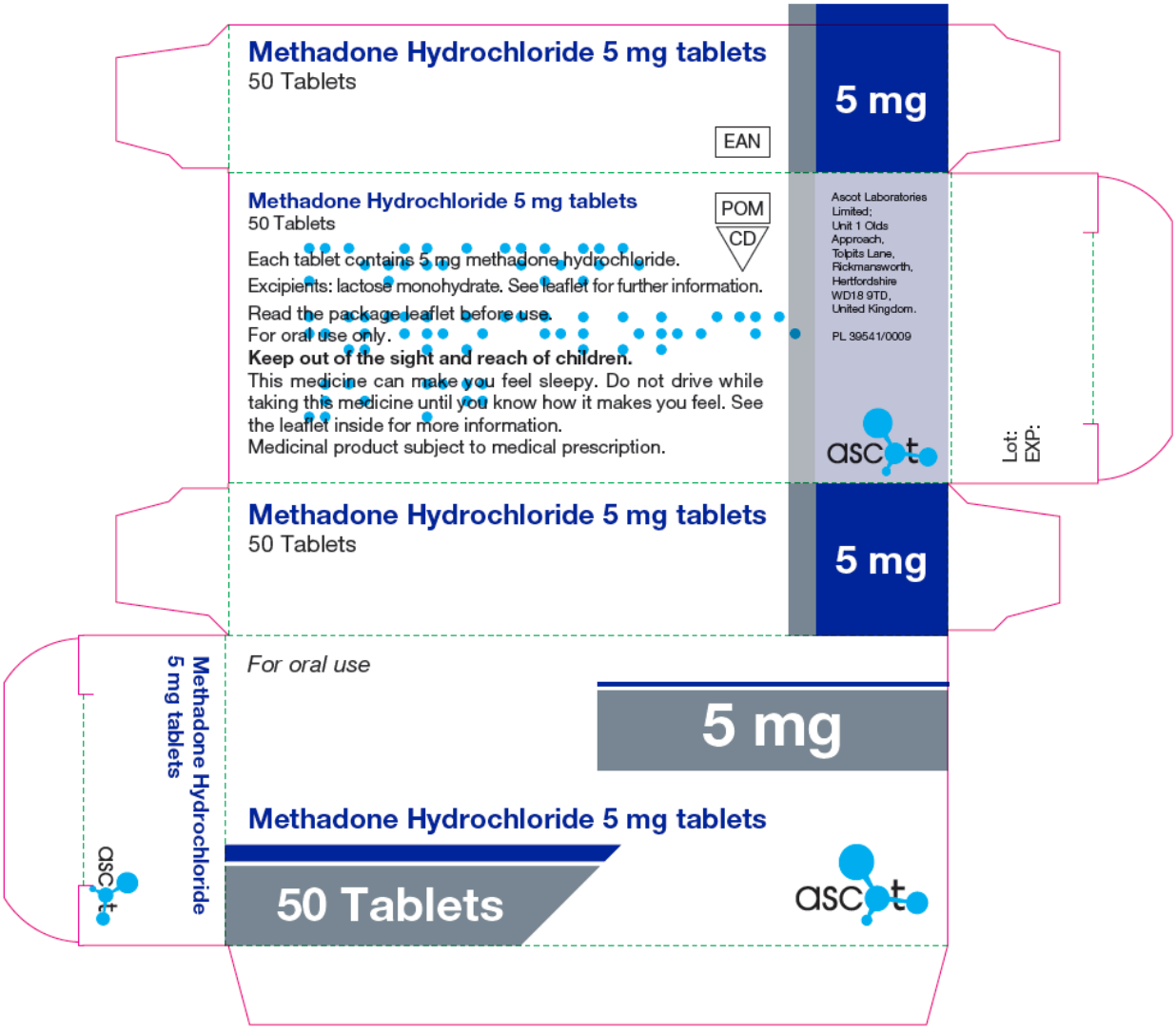
The results show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

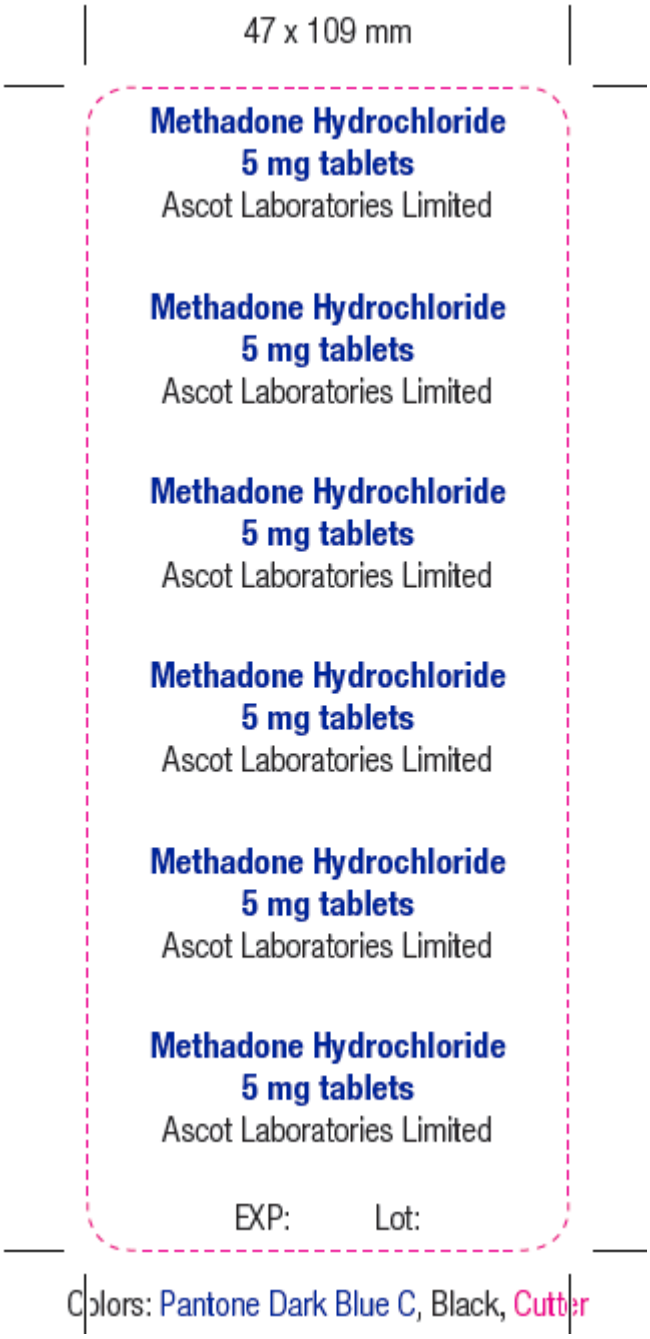
VI Overall conclusion, benefit/risk assessment and recommendation

The quality of the product is acceptable, and no new non-clinical or clinical safety concerns have been identified. Adequate 'bridging' of the bibliography-based data presented in the clinical overview to the proposed product is considered acceptable without the need for a bioequivalence study.
Extensive clinical experience with methadone hydrochloride is considered to have demonstrated the therapeutic value of the compound. The benefit-risk is, therefore, considered to be positive.

Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labels
In accordance with Directive 2010/84/EU the Summaries of Product Characteristics (SmPC) and Patient Information Leaflets (PIL) for products granted Marketing Authorisations at a national level are available on the MHRA website.

The approved labelling for Methadone Hydrochloride 5 mg tablets is presented below:




47 x 109 mm
Methadone Hydrochloride
5 mg tablets
Ascot Laboratories Limited
Methadone Hydrochloride
5 mg tablets
Ascot Laboratories Limited
Methadone Hydrochloride
5 mg tablets
Ascot Laboratories Limited
Methadone Hydrochloride
5 mg tablets
Ascot Laboratories Limited
Methadone Hydrochloride
5 mg tablets
Ascot Laboratories Limited
Methadone Hydrochloride
5 mg tablets
Ascot Laboratories Limited
EXP: Lot:
Colors: Pantone Dark Blue C, Black, Cutter

Annex 1

Table of content of the PAR update

Steps taken after the initial procedure with an influence on the Public Assessment Report (Type II variations, PSURs, commitments)

Scope	Procedure number	Product information affected	Date of start of the procedure	Date of end of procedure	Approval/ non approval	Assessment report attached Y/N (version)