Pethidine Hydrochloride 50 mg Tablets

PL 17507/0223

UKPAR

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LAY SUMMARY
Pethidine Hydrochloride 50 mg Tablets
(Pethidine hydrochloride)

This is a summary of the Public Assessment Report (PAR) for Pethidine Hydrochloride 50 mg Tablets (PL 17507/0223). It explains how Pethidine Hydrochloride 50 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 Pethidine Hydrochloride 50 mg Tablets.

For practical information about using Pethidine Hydrochloride 50 mg Tablets, patients should read the package leaflet or contact their doctor or pharmacist.

What are Pethidine Hydrochloride 50 mg Tablets and what are they used for?
Pethidine Hydrochloride 50 mg Tablets is a ‘generic’ medicine. This means that Pethidine Hydrochloride 50 mg Tablets are similar to a reference medicine already authorised in the UK called Pethidine Tablets BP 50 mg (Martindale Pharmaceuticals Limited; PL 00156/0031).

This medicine is used for the relief of moderate to severe pain including pain during labour and before and during operations.

How are Pethidine Hydrochloride 50 mg Tablets used?
Pethidine Hydrochloride 50 mg Tablets are taken by mouth.

The recommended dose for adults is 1-3 (50-150 mg) tablets as a single dose. In elderly and infirm patients a dosage of 1 tablet (50 mg) should be taken and this may be increased to 2-3 tablets once the patient’s reaction to pethidine hydrochloride is known. In children a single dose of 0.5-2 mg/kg body weight is recommended. Dosage should not be repeated more often than every four hours.

Pethidine Hydrochloride 50 mg Tablets can only be obtained on prescription from a doctor.

For further information on how Pethidine Hydrochloride 50 mg Tablets are used, please see the Summary of Product Characteristics and package leaflet available on the MHRA website.

How do Pethidine Hydrochloride 50 mg Tablets work?
Pethidine Hydrochloride 50 mg Tablets contain the active substance pethidine hydrochloride which belongs to a group of medicines called opioid analgesics. This medicine helps to relieve pain.

How have Pethidine Hydrochloride 50 mg Tablets been studied?
No clinical studies were conducted as Pethidine Hydrochloride 50 mg Tablets are generic medicines that are classified as highly soluble and highly permeable and contain the same active substance as the reference medicine, Pethidine Tablets BP 50 mg (Martindale Pharmaceuticals Limited; PL 00156/0031).

What are the benefits and risks of Pethidine Hydrochloride 50 mg Tablets?
In tests Pethidine Hydrochloride 50 mg Tablets have been shown to release pethidine hydrochloride in the same way as the reference product, Pethidine Tablets BP 50 mg, which have been used in the UK since 1995. Therefore, their benefits and risks are taken as being the same as those of the reference medicine, Pethidine Tablets BP 50 mg (Martindale Pharmaceuticals Limited; PL 00156/0031).

Why are Pethidine Hydrochloride 50 mg Tablets approved?
It was concluded that, in accordance with EU requirements, Pethidine Hydrochloride 50 mg Tablets have been shown to have comparable quality to Pethidine Tablets BP 50 mg (Martindale
Pharmaceuticals Limited; PL 00156/0031). Therefore, the view was that, as for Pethidine Tablets BP 50 mg (Martindale Pharmaceuticals Limited; PL 00156/0031), the benefit outweighs the identified risk.

**What measures are being taken to ensure the safe and effective use of Pethidine Hydrochloride 50 mg Tablets?**

A Risk Management Plan has been developed to ensure that Pethidine Hydrochloride 50 mg Tablets are used as safely as possible. Based on this plan, safety information has been included in the Summary of Product Characteristics and the package leaflet for Pethidine Hydrochloride 50 mg Tablets, including the appropriate precautions to be followed by healthcare professionals and patients.

**Other information about Pethidine Hydrochloride 50 mg Tablets**

A Marketing Authorisation was granted in the UK on 23rd September 2014.

The full PAR for Pethidine Hydrochloride 50 mg Tablets follows this summary.

For more information about treatment with Pethidine Hydrochloride 50 mg Tablets, read the package leaflet, or contact your doctor or pharmacist.

This summary was last updated in November 2014.
Pethidine Hydrochloride 50 mg Tablets

PL 17507/0223

SCIENTIFIC DISCUSSION

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INTRODUCTION

The Medicines and Healthcare products Regulatory Agency (MHRA) granted a Marketing Authorisation to Auden Mckenzie (Pharma Division) Ltd for the medicinal product Pethidine Hydrochloride 50 mg Tablets (PL 17507/0223) on 23rd September 2014. This is a prescription-only medicine (POM) used for the following indications:

- Obstetric analgesia
- Moderate to severe pain
- Premedication and analgesia during anaesthesia

This application was submitted as a national abridged application under Article 10(1) of Directive 2001/83/EC, as amended. The applicant has cross-referred to Pethidine Tablets BP 50 mg, authorised to Martindale Pharmaceuticals Limited (PL 00156/0031) on 28th September 1995. Prior to this, the product was licensed to Roche Products Limited (PL 00031/5103R) for which the licence has been cancelled.

Pethidine hydrochloride is a phenylpiperidine synthetic opioid analgesic. Pethidine is predominantly a μ-receptor opioid agonist and it exerts its chief pharmacological action on the central nervous system (CNS) and on the neural elements in the bowel.

No non-clinical or clinical studies were conducted, which is acceptable given that reference is made to a medicinal product which has been licensed for over 10 years. Satisfactory dissolution data are provided for this medicine which has the same qualitative and quantitative composition in terms of drug substance and a similar qualitative composition in terms of excipients as the reference product.

The MHRA has been assured that acceptable standards of Good Manufacturing Practice are in place for this product type at all sites responsible for the manufacture, assembly and batch release of the product.
**PHARMACEUTICAL ASSESSMENT**

**ACTIVE SUBSTANCE**

INN: Pethidine hydrochloride

Chemical name: Ethyl 1-methyl-4-phenylpiperidine-4-carboxylate hydrochloride

Structure:

![Chemical Structure of Pethidine Hydrochloride]

Molecular formula: C_{15}H_{22}ClNO_{2}

Molecular weight: 283.8 g/mol

Appearance: White or almost white, crystalline powder

Solubility: Very soluble in water and freely soluble in alcohol.

Pethidine hydrochloride is the subject of a European Pharmacopoeia monograph.

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

**DRUG PRODUCT**

**Other Ingredients**

Other ingredients consist of the pharmaceutical excipients maize starch, lactose monohydrate, sucrose, talc, magnesium stearate and acacia. Appropriate justification for the inclusion of each excipient has been provided.

All excipients comply with their respective Pharmacopoeia monographs. Satisfactory Certificates of Analysis have been provided for all excipients showing compliance with the proposed specifications.

The only excipient used that contains material of animal or human origin is lactose monohydrate. The applicant has provided a declaration that the milk used in the production of lactose monohydrate is sourced from healthy animals under the same conditions as that for human consumption. Confirmation has also been given that the magnesium stearate used in the tablets is of vegetable origin.

**Pharmaceutical Development**

The objective of the development programme was to formulate robust, stable, tablets containing pethidine hydrochloride that could be considered as a generic medicinal product of Pethidine Tablets BP 50 mg (Martindale Pharmaceuticals Limited).

Comparable dissolution and impurity profiles are provided for this product versus the originator product.

**Manufacturing Process**

A satisfactory batch formula has been provided for the manufacture of the product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated with pilot-scale batches and has shown satisfactory results. The applicant has committed to perform process validation studies on future full-scale production batches.
Control of Finished Product
The finished product specification is satisfactory. The test methods have been described and adequately validated, as appropriate. Batch data have been provided that comply with the release specifications. Certificates of Analysis have been provided for any working standards used.

Container Closure System
The product is packed in polyvinylchloride/polyvinylidenechloride/aluminium blisters containing 50 tablets.

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.

Stability
Finished product stability studies were performed in accordance with current guidelines on batches of finished product packed in the packaging proposed for marketing. The data from these studies support a shelf-life of 24 months, with no special storage conditions.

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

Bioequivalence
Pethidine has high solubility and high permeability and is classified as Biopharmaceutics Classification System (BCS) class I. Therefore, a bioequivalence study has not been performed between the reference and the proposed products. Dissolution data comparing the test product, Pethidine Hydrochloride 50 mg Tablets, with the reference product, Pethidine Tablets BP 50 mg, are provided in place of a bioequivalence study and the two medicinal products were found to have comparable dissolution profiles.

Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labelling
The SmPC, PIL and labelling are satisfactory from a pharmaceutical perspective.

User testing of the package leaflet has been accepted, based on bridging reports provided by the applicant making reference to the user-testing of the PIL for Pethidine 50 mg/ml Solution for Injection (parent PIL). The products are from the same therapeutic class and have similar indications. A critical analysis demonstrated that the key messages for safe and effective use for both leaflets were similar. The justification on the rationale for bridging is accepted.

Marketing Authorisation Application (MAA) Form
The MAA form is satisfactory from a pharmaceutical perspective.

Expert Report/Quality Overall Summary
The quality overall summary is written by an appropriately qualified person and is a suitable summary of the pharmaceutical aspects of the dossier.

Conclusion
The grant of a Marketing Authorisation is recommended.
NON-CLINICAL ASSESSMENT

The pharmacodynamic, pharmacokinetic and toxicological properties of pethidine hydrochloride are well-known. Thus, the applicant has not provided additional studies and further studies are not required.

A non-clinical overview has been provided, written by an appropriately qualified person. This is satisfactory.

A suitable justification has been provided for not submitting an environmental risk assessment.

There are no objections to the approval of this product from a non-clinical point of view.
CLINICAL ASSESSMENT

Clinical Pharmacology
Bioequivalence studies are not necessary to support this application as the applicant applies for a bio pharmaceutics classification system (BCS)-based biowaiver in line with the bioequivalence guideline (CPMP/EWP/QWP/1401/98 Rev 1/Corr**, Appendix III). The applicant has provided detailed justification and discussion to support this exemption in the clinical dossier.

Pharmacodynamics
No new data have been submitted and none are required for applications of this type.

Efficacy
No new data have been submitted and none are required for applications of this type.

Safety
No new safety data have been submitted and none are required for applications of this type.

Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and labelling
The SmPC, PIL and labelling are satisfactory from a clinical perspective and consistent with those for the reference product.

Pharmacovigilance System and Risk Management Plan
The Pharmacovigilance System, as described by the applicant, fulfils the requirements and provides adequate evidence that the applicant has access to the services of a qualified person responsible for pharmacovigilance, and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

A suitable risk management plan has been provided for this product.

Clinical Expert Report/Overall Summary
The clinical expert report is written by an appropriately qualified physician and is a suitable summary of the clinical aspects of the dossier.

Marketing Authorisation Application (MAA) Form
The MAA form is satisfactory from a clinical perspective.

Conclusion
There are no objections to the approval of this product from a clinical point of view.
OVERALL CONCLUSION AND BENEFIT/RISK ASSESSMENT

QUALITY
The important quality characteristics of Pethidine Hydrochloride 50 mg Tablets are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

NON-CLINICAL
No new non-clinical data were submitted and none are required for this type of application.

CLINICAL
No new clinical data were submitted and none are required for this type of application.

No new or unexpected safety concerns arose from this application.

PRODUCT LITERATURE
The SmPC, PIL and labelling are satisfactory and consistent with those for the reference product.

BENEFIT RISK ASSESSMENT
The quality of the product is acceptable and no new non-clinical or clinical concerns have been identified. Extensive clinical experience with pethidine hydrochloride is considered to have demonstrated the therapeutic value of the compound. The benefit risk assessment is, therefore, considered to be positive.
**Pethidine Hydrochloride 50 mg Tablets**

**PL 17507/0223**

## STEPS TAKEN FOR ASSESSMENT

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<th>Description</th>
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<tbody>
<tr>
<td>1</td>
<td>The MHRA received the Marketing Authorisation application on 4\textsuperscript{th} February 2014</td>
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<tr>
<td>2</td>
<td>Following standard checks and communication with the applicant the MHRA considered the application valid on 11\textsuperscript{th} February 2014</td>
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<tr>
<td>3</td>
<td>Following assessment of the application the MHRA requested further information on the dossier on 21\textsuperscript{st} May 2014</td>
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<tr>
<td>4</td>
<td>The applicant responded to the MHRA’s request, providing further information on 25\textsuperscript{th} June 2014</td>
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<tr>
<td>5</td>
<td>The application was determined on 23\textsuperscript{rd} September 2014</td>
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SUMMARY OF PRODUCT CHARACTERISTICS

In accordance with Directive 2010/84/EU, the Summaries of Product Characteristics (SmPCs) for products granted Marketing Authorisations at a national level are available on the MHRA website.
PATIENT INFORMATION LEAFLET

In accordance with Directive 2010/84/EU, the Patient Information Leaflets (PILs) for products granted Marketing Authorisations at a national level are available on the MHRA website.