Medicines & Healthcare products
Regulatory Agency

Public Assessment Report

National Procedure

Pethidine hydrochloride 50 mg/ml solution for injection

pethidine hydrochloride

PL 56639/0005

SVP Pharma Ltd

LAY SUMMARY

Pethidine hydrochloride 50 mg/ml solution for injection
pethidine hydrochloride

This is a summary of the Public Assessment Report (PAR) for Pethidine hydrochloride 50 mg/ml solution for injection. It explains how this product was assessed and its authorisation recommended, as well as its conditions of use. It is not intended to provide practical advice on how to use this product.

This product will be referred to as Pethidine in this lay summary for ease of reading.

For practical information about using Pethidine, patients should read the Patient Information Leaflet (PIL) or contact their doctor or pharmacist.

What is Pethidine and what is it used for?
This product is a generic medicine. This means that this medicine is the same as, and considered interchangeable with, a reference medicine already authorised, called Pethidine 50mg/ml & 100mg/2ml Solution for Injection.

Pethidine has been prescribed to the patient for relief of moderate to severe pain. Including pain associated with childbirth, or during an anaesthetic or following an operation. As well as relieving pain, pethidine has other effects including a sedative (calming) effect.

This medicine has been prescribed to the patient and should not be given to anyone else. Opioids can cause addiction, and the patient may get withdrawal symptoms if they stop taking it suddenly. Their prescriber should have explained how long they will be taking it for and when it is appropriate to stop, how to do this safely.

How does Pethidine work?
Pethidine belongs to a group of medicines called opioid analgesics.

It contains pethidine which belongs to a class of medicines called opioids, which are ‘pain relievers. An analgesic is a medicine that can be used to relieve pain.

How is Pethidine used?
The pharmaceutical form of this medicine is a solution for injection, and the route of administration is subcutaneous (into the tissue just below the skin), intramuscular (into a muscle) or slow intravenous (into a vein) use.

The patient’s prescriber should have discussed with them, how long the course of injection will last. The doctor will arrange a plan for stopping treatment. This will outline how to gradually reduce the dose and stop taking the medicine.

Adults:
A single dose of between 25 – 100 mg may be injected into a muscle or into the tissue just beneath the skin. For injection into a vein, a single dose of between 25 – 50 mg may be given slowly. These single doses should not usually be repeated more frequently than every 4 hours if required.

Elderly Patients or for Patients in a Weakened Condition:
The initial dose should not exceed 25mg, because elderly patients or those in a weakened condition are more sensitive to the unwanted effects of pethidine.

Use in children
The usual single dose is 0.5 to 2.0mg per kilogram of body weight by injection into a muscle. If necessary, this dose may be repeated, allowing at least 4 hours between doses.
To ensure that the correct dose is given, use of a special syringe with fine markings is recommended for administration in children. Alternatively, the solution may be diluted in Water for Injections to make it easier to measure the dose accurately.

For further information on how Pethidine is used, refer to the PIL and Summary of Product Characteristics (SmPC) available on the Medicines and Healthcare products Regulatory Agency (MHRA) website.

This medicine can only be obtained with a prescription.

The patient should ask the administering healthcare practitioner if they have any questions concerning their medicine.

What benefits of Pethidine have been shown in studies?
Pethidine is a generic medicine that fulfils criteria meaning that no additional studies are required. Pethidine has been considered a generic medicine of the reference medicine based on a comparison of their physical and chemical characteristics.

What are the possible side effects of Pethidine?
For the full list of all side effects reported with this medicine, see Section 4 of the PIL or the SmPC available on the MHRA website.

If a patient gets any side effects, they should talk to their doctor, pharmacist or nurse. This includes any possible side effects not listed in the product information or the PIL that comes with the medicine. Patients can also report suspected side effects themselves, or a report can be made on their behalf by someone else who cares for them, directly via the Yellow Card scheme at https://yellowcard.mhra.gov.uk or search for 'MHRA Yellow Card' online. By reporting side effects, patients can help provide more information on the safety of this medicine.

Because Pethidine is a generic medicine, its benefits and possible side effects are considered to be the same as for the reference medicine.

Why was Pethidine approved?
It was concluded that, Pethidine has been shown to be comparable to the reference medicine. Therefore, the MHRA decided that, as for the reference medicine, the benefits are greater than the risks and authorised that it can be approved for use.

What measures are being taken to ensure the safe and effective use of Pethidine?
As for all newly-authorised medicines, a Risk Management Plan (RMP) has been developed for Pethidine. The RMP details the important risks of Pethidine, how these risks can be minimised, any uncertainties about Pethidine (missing information), and how more information will be obtained about the important risks and uncertainties.

The following safety concerns have been recognised for Pethidine:

Summary of safety concerns	
Important identified risks	– Dependence, abuse, tolerance and withdrawal – Overdose
Important potential risks	None.
Missing information	None.

The information included in the SmPC and the PIL is compiled based on the available quality, non-clinical and clinical data, and includes appropriate precautions to be followed by healthcare professionals and patients. Side effects of Pethidine are continuously monitored and reviewed including all reports of suspected side-effects from patients, their carers, and healthcare professionals.

An RMP and a summary of the pharmacovigilance system have been provided with this application and are satisfactory.

Other information about Pethidine
A marketing authorisation Pethidine was granted in the United Kingdom (UK) on 31 October 2024.

The full PAR for Pethidine follows this summary.

This summary was last updated in December 2024.

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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) considered that the application for Pethidine hydrochloride 50 mg/ml solution for injection (PL 56639/0005) could be approved.

The product is approved for the following indication:
As an analgesic for the relief of moderate to severe pain including obstetric analgesia; pre-operative medication and analgesia during anaesthesia; post-operative analgesia.

Pethidine hydrochloride 50 mg/ml solution for injection contains the active substance, pethidine, which is a synthetic opioid analgesic similar to morphine although less potent and shorter acting. Its analgesic effect usually lasts for 2 to 4 hours. The analgesic effect occurs after about 10 minutes following parenteral administration. It acts on the CNS system and smooth muscles via the peripheral nervous system. However, it has a weaker action on smooth muscle than morphine and therefore has less effect on cough, bowel motility, biliary tone and secretion of pituitary hormones. Pethidine also causes the release of histamine from mast cells resulting in a number of allergic-type reactions.

This application was approved under Regulation 51B of The Human Medicines Regulation 2012, as amended (previously Article 10(1) of Directive 2001/83/EC, as amended), as a generic medicine of a suitable originator medicinal product, Pethidine 50mg/ml & 100mg/2ml Solution for Injection that has been licensed for a suitable time, in line with the legal requirements.

No new non-clinical studies were conducted, which is acceptable given that the application is for a generic medicinal product of a suitable reference product.

A biowaiver was submitted with this application, which was accepted. A bioequivalence study was not necessary to support this application for a parenteral product and the applicant submitted none. According to CPMP guidelines, bioequivalence studies are not generally required for parenteral aqueous solutions (CPMP/EWP/QWP/1401/98 Rev. 1/Corr**, Guideline on the Investigation of Bioequivalence).

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

A Risk Management Plan (RMP) and a summary of the pharmacovigilance system have been provided with this application and are satisfactory.

A marketing authorisation for Pethidine hydrochloride 50 mg/ml solution for injection was granted in the United Kingdom (UK) on 31 October 2024.

II QUALITY ASPECTS

II.1 Introduction

The active substance is pethidine hydrochloride.
Each ml of solution for injection contains 50 mg of pethidine hydrochloride.

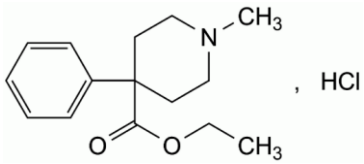
In addition to pethidine hydrochloride, this product also contains the following excipients: hydrochloric acid, sodium hydroxide and water for injections.

The finished product is packaged in 1 ml or 2 ml colourless, type I glass ampoules and are available in pack-sizes of 10 ampoules. 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 regulations concerning materials in contact with food.

II.2 ACTIVE SUBSTANCE

rINN: Pethidine hydrochloride
Chemical Name: Ethyl 1-methyl-4-phenylpiperidine-4-carboxylate hydrochloride.
Molecular Formula: $C_{15}H_{22}ClNO_2$
Chemical Structure:



Molecular Weight: 283.8
Appearance: White or almost white crystalline powder.
Solubility: Very soluble in water, freely soluble in ethanol (96 per cent).

Pethidine hydrochloride is the subject of a European Pharmacopoeia monograph.

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

II.3 DRUG PRODUCT

Pharmaceutical development

A satisfactory account of the pharmaceutical development was provided.

Comparative *in vitro* impurity profiles were provided for the proposed and reference products.

All excipients comply with either their respective European/national monographs, or a suitable in-house specification. Satisfactory Certificates of Analysis were provided for all excipients.

No excipients of animal or human origin are used in the final products.

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

Manufacture of the product

A description and flow-chart of the manufacturing method has been provided.

Satisfactory batch formulation data have been provided for the manufacture of the product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated and has shown satisfactory results.

Finished Product Specifications
The finished product specifications at release and shelf-life are satisfactory. The test methods have been described and adequately validated. Batch data have been provided that comply with the release specifications. Certificates of Analysis have been provided for any working standards used.

Stability
Finished product stability studies have been conducted in accordance with current guidelines, using batches of the finished product stored in the packaging proposed for marketing. Based on the results, a shelf-life of 3 years, with the storage conditions 'Do not store above 25ºC', is acceptable.

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

II.4 Discussion on chemical, pharmaceutical and biological aspects
The grant of a marketing authorisation was recommended.

III NON-CLINICAL ASPECTS

III.1 Introduction
As the pharmacodynamic, pharmacokinetic and toxicological properties of pethidine hydrochloride are well-known, no new non-clinical studies are required, and none have been provided. An overview based on the literature review is, thus, appropriate.

III.2 Pharmacology
No new pharmacology data were provided, and none were required for this application.

III.3 Pharmacokinetics
No new pharmacokinetic data were provided, and none were required for this application.

III.4 Toxicology
No new toxicology data were provided, and none were required for this application.

III.5 Ecotoxicity/Environmental Risk Assessment
A suitable justification was provided for non-submission of an Environmental Risk Assessment. As the application is for generic version of an already authorised product, an increase in environmental exposure is not anticipated following approval of the marketing authorisation for the proposed product.

III.6 Discussion on the non-clinical aspects
The grant of a marketing authorisation was recommended.

IV CLINICAL ASPECTS

IV.1 Introduction

The clinical pharmacology, efficacy and safety of pethidine is well-known. According to the regulatory requirements, the applicant has provided a suitable biowaiver and a bioequivalence study is not required for this product. An overview based on a literature review is, thus, satisfactory.

IV.2 Pharmacokinetics

No new pharmacokinetic data were submitted for this application, and none were required.

IV.3 Pharmacodynamics

No new pharmacodynamic data were submitted for this application and none were required.

IV.4 Clinical efficacy

No new efficacy data were submitted with this application, and none were required.

IV.5 Clinical safety

No new safety data were submitted with this application, and none were required. The safety profile for this product is considered to be the same as Pethidine 50mg/ml & 100mg/2ml Solution for Injection.

IV.6 Risk Management Plan (RMP)

The applicant has submitted an RMP, in accordance with the requirements of Regulation 182 of The Human Medicines Regulation 2012, as amended. The applicant proposes only routine pharmacovigilance and routine risk minimisation measures for all safety concerns. This is acceptable.

IV.7 Discussion on the clinical aspects

The grant of a marketing authorisation was recommended for this application.

V USER CONSULTATION

A full colour mock-up of the Patient Information Leaflet (PIL) was provided with the application in accordance with legal requirements, including user consultation.

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. Extensive clinical experience with pethidine hydrochloride is considered to have demonstrated the therapeutic value of the compound. The benefit/risk is, therefore, considered to be positive.

The Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and labelling are satisfactory, in line with current guidelines and consistent with the reference product.

In accordance with legal requirements, the current approved UK version of the SmPC and PIL for this product are available on the MHRA website.

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Steps taken after the initial procedure with an influence on the Public Assessment Report (non-safety variations of clinical significance).

Please note that only non-safety variations of clinical significance are recorded below and in the annexes to this PAR. The assessment of safety variations where significant changes are made are recorded on the MHRA website or European Medicines Agency (EMA) website. Minor changes to the marketing authorisation are recorded in the current SmPC and/or PIL available on the MHRA website.

Application type	**Scope**	**Product information affected**	**Date of grant**	**Outcome**	**Assessment report attached Y/N**