Ketamine 50 mg/ml Injection

(ketamine hydrochloride)

PL 01502/0099

hameln pharmaceuticals ltd

UKPAR
LAY SUMMARY

Ketamine 50 mg/ml Injection
(ketamine hydrochloride)

This is a summary of the Public Assessment Report (PAR) for Ketamine 50 mg/ml Injection (PL 01502/0099). It explains how the application for Ketamine 50 mg/ml Injection was assessed and its authorisation recommended, as well as the conditions of use. It is not intended to provide practical advice on how to use Ketamine 50 mg/ml Injection.

The product may be referred to as ‘Ketamine Injection’ or ‘Ketamine’ in this report.

For practical information about using Ketamine Injection, patients should read the package leaflet or contact their doctor or pharmacist.

What is Ketamine Injection and what is it used for?
Ketamine Injection is a ‘generic medicine’. This means that Ketamine Injection is similar to a ‘reference medicine’ already authorised in the European Union (EU) called Ketalar 50mg/ml Injection (Pfizer Limited, UK), which was first authorised in the UK on 31 October 1997.

Ketamine Injection is an anaesthetic agent, which is used to put patients to sleep during an operation. Ketamine may be used in both routine and emergency surgery. This medicine is used in adults, the elderly and children. Ketamine can be given alone or in combination with other anaesthetic agents.

How does Ketamine Injection work?
This medicine contains ketamine hydrochloride which belongs to a group of medicines called anaesthetic agents, which act in the brain to put patients to sleep during an operation.

How is Ketamine Injection used?
Except in an emergency, Ketamine should only be used in hospitals by experienced anaesthetists with resuscitation equipment available.

Ketamine Injection is available as a solution for injection or infusion. The product is given by injection or infusion into a vein or a muscle by a doctor or nurse.

Before an operation the patient will usually be given a medicine such as atropine or hyoscine to dry up secretions (body fluids like saliva and tears) and another medicine called a benzodiazepine. The benzodiazepine will help the patient to relax and help to prevent a side effect known as "emergence reaction".

The dose of Ketamine given depends on its use and varies from person to person. When injected directly into a vein at a dose of 2 mg for every kg of bodyweight, Ketamine produces unconsciousness within 30 seconds and this lasts for 5 to 10 minutes. Because it works so quickly, it is important that the patient is lying down, or is supported in some other way when the drug is given. When Ketamine is injected into a muscle, at a dose of 10 mg for every kg of bodyweight, it takes longer to work (3 to 4 minutes) but lasts 12 to 25 minutes.

The anaesthetist will then keep the patient anaesthetised with either:
• another anaesthetic
• more Ketamine given by injection into a muscle or vein, or in a drip (infusion)
• Ketamine together with another anaesthetic.

When it is injected directly into a vein, Ketamine is given over at least a minute so that it does not slow the patient’s breathing too much. If breathing is slowed, it can be helped mechanically.

While the patient is anaesthetised, the anaesthetist will watch over the patient constantly, paying particular attention to the patient’s breathing, airways, reflexes, the degree of anaesthesia and the condition of the heart.

Please read section 3 of the package leaflet (PL) for detailed information on dosing recommendations, the route of administration, and the duration of treatment.

Ketamine Injection can only be obtained on prescription and, except for in emergency, is for use only in hospitals.

What benefits of Ketamine Injection have been shown in studies?
Studies in patients have been limited to tests to determine that the applicant’s Ketamine 50 mg/ml Injection is similar to the reference medicine Ketalar 50mg/ml Injection (Pfizer Limited Ltd). Two medicines are bioequivalent when they produce the same levels of the active substance in the body.

What are the possible side effects from Ketamine Injection?
Like all medicines, Ketamine Injection can cause side effects, although not everybody gets them.

For the full list of all side effects reported with Ketamine Injection, see section 4 of the package leaflet or the Summary of Product Characteristics available on the MHRA website.

Also, for the full list of restrictions, see the package leaflet.

Why is Ketamine Injection approved?
The MHRA decided that the benefits outweigh the identified risks and recommended that Ketamine Injection can be approved for use.

What measures are being taken to ensure the safe and effective use of Ketamine Injection?
A Risk Management Plan has been developed to ensure that Ketamine Injection is 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 Ketamine Injection, 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 Ketamine Injection.
A Marketing Authorisation was granted in the UK on 01 July 2015.

The full PAR for Ketamine Injection follows this summary.

For more information about treatment with Ketamine Injection, read the package leaflet, or contact your doctor or pharmacist.

This summary was last updated in August 2015.
Ketamine 50mg/ml Injection
(ketamine hydrochloride)

PL 01502/0099

SCIENTIFIC DISCUSSION

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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 hameln pharmaceuticals ltd a Marketing Authorisation for the medicinal product Ketamine 50 mg/ml Injection (PL 01502/0099) on 01 July 2015. The product is a Prescription Only Medicine (POM).

Ketamine 50 mg/ml Injection may be used:
- as an anaesthetic agent for diagnostic and surgical procedures. When used by intravenous or intramuscular injection, Ketamine is best suited for short procedures. With additional doses, or by intravenous infusion, Ketamine can be used for longer procedures. If skeletal muscle relaxation is desired, a muscle relaxant should be used and respiration should be supported.
- for the induction of anaesthesia prior to the administration of other general anaesthetic agents;
- to supplement other anaesthetic agents.

Specific areas of application or types of procedures:
- when the intramuscular route of administration is preferred;
- debridement, painful dressings, and skin grafting in burned patients, as well as other superficial surgical procedures;
- neurodiagnostic procedures such as pneumoencephalograms, ventriculograms, myelograms, and lumbar punctures;
- diagnostic and operative procedures of the eye, ear, nose, and mouth, including dental extractions (Note: Eye movements may persist during ophthalmological procedures);
- anaesthesia in poor-risk patients with depression of vital functions or where depression of vital functions must be avoided, if at all possible;
- orthopaedic procedures such as closed reductions, manipulations, femoral pinning, amputations, and biopsies;
- sigmoidoscopy and minor surgery of the anus and rectum, circumcision and pilonidal sinus. Cardiac catheterization procedures;
- Caesarian section; as an induction agent in the absence of elevated blood pressure;
- anaesthesia in the asthmatic patient, either to minimise the risks of an attack of bronchospasm developing, or in the presence of bronchospasm where anaesthesia cannot be delayed.

The application was submitted under Article 10(1) of Directive 2001/83/EC, as amended, claiming to be a generic medicinal product of the originator product Ketalar 50mg/ml Injection (Pfizer Limited, UK), which was first authorised in the UK on 31 October 1997.

Ketamine Injection contains the active ingredient ketamine (as ketamine hydrochloride), which is a rapidly acting general anaesthetic for intravenous or intramuscular use with a distinct pharmacological action. Ketamine induces sedation, immobility, amnesia and marked analgesia. The anaesthetic state produced by ketamine has been termed “dissociative anaesthesia” in that it appears to selectively interrupt association pathways of the brain before producing somesthetic sensory blockade.

No new non-clinical studies were performed, which is acceptable given that the application was based on being a generic medicinal product of an originator product that has been in clinical use for over 10 years.
No new clinical data have been submitted and none are required for an application of this type. A bioequivalence study was not necessary to support this application for an aqueous parenteral product, containing the same active substance as the reference product.

No new or unexpected safety concerns arose during review of information provided by the Marketing Authorisation Holder and it was, therefore, judged that the benefits of Ketamine 50 mg/ml Injection outweigh the risks and a Marketing Authorisation was granted.

II QUALITY ASPECTS

II.1 Introduction

The application is submitted in accordance with Article 10(1) of Directive 2001/83/EC, as amended.

The quality overall summary has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical aspects of the dossier.

The product is available as a clear solution for injection or infusion.

Each 1 ml of solution for injection or infusion contains ketamine hydrochloride equivalent to 50 mg ketamine base. The other ingredients consist of benzethonium chloride and water for injections.

The finished product is supplied in Type I clear glass vials. The product is available in pack sizes of 1 or 10 glass vials of 10 ml of solution. Not all pack sizes may be marketed.

Satisfactory specifications and Certificates of Analysis have been provided for the primary packaging components. All primary packaging comply with suitable Ph.Eur requirements for containers and closures for parenteral preparations.

II.2 Drug Substance

Ketamine hydrochloride

INN: Ketamine hydrochloride
Chemical name: (2RS)-2-(2-Chlorophenyl)-2-(methylamino)cyclohexanone hydrochloride.
Structure:

![Structure of Ketamine hydrochloride]

Molecular formula: C₁₃H₁₇Cl₂NO
Mr: 274.2
Appearance: A white or almost white, crystalline powder.
Solubility: Freely soluble in water and in methanol and soluble in ethanol (96%).

Ketamine hydrochloride is the subject of a European Pharmacopoeia monograph.

All aspects of the manufacture and control of the active substance, ketamine hydrochloride, are covered by a European Directorate for the Quality of Medicines and Healthcare (EDQM) Certificate of Suitability.
II.3 Medicinal Product

Pharmaceutical Development
The objective of the development programme was to formulate a safe, efficacious, stable, solution containing 50 mg/ml of ketamine (as hydrochloride) that could be considered a generic medicinal product of the reference product Ketalar 50mg/ml Injection (Pfizer Limited). Suitable pharmaceutical development data have been provided.

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

None of the excipients contain materials of animal or human origin.

No genetically modified organisms (GMO) have been used in the preparation of these excipients.

Manufacturing Process
A satisfactory batch formula has been provided for the manufacture of the product, along with an appropriate description of the manufacturing process. The manufacturing process has been validated at production scale and has shown satisfactory results.

Control of Finished Product
The finished product specification is acceptable. Test methods have been described that have been validated adequately. Batch data have been provided that complies with the release specification. 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 finished product in the packaging proposed for marketing. Based on the results, a shelf-life of 3 years for the unopened has been approved, with the special storage conditions ‘This medicinal product does not require any special temperature storage conditions. Do not freeze. Store in the original container’.

The product is for single use only. Any unused product should be discarded. After dilution the solution should be used immediately.

Suitable post approval stability commitments have been provided.

Bioequivalence/Bioavailability
A bioequivalence study was not necessary to support this type of application for a parenteral product.

II.4 Discussion on chemical, pharmaceutical and biological aspects
It is recommended that a Marketing Authorisation is granted for this application for Ketamine 50 mg/ml Injection.

II.5 Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labels
The SmPC, PIL and labelling are satisfactory and, where appropriate, in line with current guidance.
III NON-CLINICAL ASPECTS

III.1 Introduction
The pharmacodynamic, pharmacokinetic and toxicological properties of ketamine are well known and are adequately described in the applicant’s non-clinical overview. No new non-clinical data were submitted and none are required for this type of application.

The non-clinical overview 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 Pharmacodynamics
The pharmacodynamic properties of ketamine are well known and are adequately described in the applicant’s non-clinical overview.

III.3 Pharmacokinetics
The pharmacokinetic properties of ketamine are well known and are adequately described in the applicant’s non-clinical overview.

III.4 Toxicology
The toxicological properties of ketamine are well known and are adequately described in the applicant’s non-clinical overview.

III.5 Ecotoxicity/Environmental Risk Assessment (ERA)
The Marketing Authorisation holder has provided adequate justification for not submitting an Environmental Risk Assessment (ERA). As the application is for a generic version of an already authorised product, it is not expected that environmental exposure will increase following approval of the Marketing Authorisation for the proposed product. An environmental risk assessment is therefore not deemed necessary.

III.6 Discussion on the non-clinical aspects
It is recommended that a Marketing Authorisation is granted for Ketamine 50 mg/ml Injection, from a non-clinical point of view.

IV. CLINICAL ASPECTS

IV.1 Introduction
The clinical pharmacology of ketamine is well-known. No new clinical pharmacokinetic data have been submitted and none are required for this type of application. A bioequivalence study was not necessary to support this application for an aqueous parenteral product. According to CPMP guidelines, bioequivalence studies are not generally required for parenteral aqueous solutions containing the same active substance as the currently approved product (CPMP/EWP/QWP/1401/98 Rev. 1/Corr**, Guideline on the Investigation of Bioequivalence).

The applicant’s clinical overview has been written by an appropriately qualified person and is considered acceptable.

IV.2 Pharmacokinetics
The pharmacokinetic properties of ketamine are well known and are adequately described in the applicant’s non-clinical overview. No new pharmacokinetic data were submitted and none are required for an application of this type.
IV.3 Pharmacodynamics
The clinical pharmacodynamics properties of ketamine are well-known. No new pharmacodynamic data were submitted and none are required for an application of this type.

IV.4 Clinical Efficacy
No new efficacy data have been submitted and none are required for this application for a parenteral product. The clinical efficacy of ketamine is well-known. Efficacy is adequately reviewed in the clinical overview.

IV.5 Clinical Safety
No new safety data have been submitted with this application and none are required. No new or unexpected safety concerns arose from this application.

IV.6 Risk Management Plan
The MAH has submitted a risk management plan, 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 Ketamine 50 mg/ml Injection.

<table>
<thead>
<tr>
<th>Summary of safety concerns</th>
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<td>Important identified risks</td>
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Routine pharmacovigilance and routine risk minimisation are proposed for all safety concerns. No additional risk minimisation activities were required beyond those included in the product information.

IV.7 Discussion of the clinical aspects
It is recommended that a Marketing Authorisation is granted for this application.
V. USER CONSULTATION
A 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, as amended. The language used for the purpose of user testing the pack leaflet 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 AND BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

QUALITY
The important quality characteristics of Ketamine 50 mg/ml Injection 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 an application of this type as the pharmacokinetics, pharmacodynamics and toxicology of ketamine are well-known.

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

SAFETY
The safety profile of ketamine is well-known. No new or unexpected safety issues or concerns arose from this application.

BENEFIT/RISK ASSESSMENT
The quality of the product is acceptable and no new non-clinical or clinical safety concerns have been identified. Extensive clinical experience with ketamine is considered to have demonstrated the therapeutic value of the compound. The benefit/risk assessment is, therefore, considered to be positive.

RECOMMENDATION
The grant of a Marketing Authorisation is recommended.

In accordance with Directive 2010/84/EU the Summaries of Product Characteristics (SmPCs) and Patient Information Leaflets (PILs) for products granted Marketing Authorisations at a national level are available on the MHRA website. The approved labelling is presented below:
### STEPS TAKEN AFTER THE INITIAL PROCEDURE - SUMMARY

<table>
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<th>Date submitted</th>
<th>Application type</th>
<th>Scope</th>
<th>Outcome</th>
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<tbody>
<tr>
<td>08 March 2016</td>
<td>Type IB</td>
<td>To update the Summary of Product Characteristics (SmPC) in section 4.2 (posology and administration) to include additional information regarding dosage in obstetrics, section 4.6 (Fertility, pregnancy and lactation) and section 5.2 (Pharmacokinetics) in line with the reference product Ketalar 50 mg/ml Injection (Pfizer Limited). Consequently, the Patient Information Leaflet (PIL) has been updated.</td>
<td>Approved on 18 March 2016</td>
</tr>
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</table>
ANNEX 1

Our Reference: PL 01502/0099, Application 0004
Product: Ketamine 50mg/ml Injection
Marketing Authorisation Holder: hameln pharmaceuticals ltd.
Active Ingredient(s): Ketamine Hydrochloride.

Type of Procedure: National
Submission Type: Variation
Submission Category: Type IB
Submission Complexity: Standard

Reason:
To update the Summary of Product Characteristics (SmPC) in section 4.2 (posology and administration) to include additional information regarding dosage in obstetrics, section 4.6 (Fertility, pregnancy and lactation) and section 5.2 (Pharmacokinetics) in line with the reference product Ketalar 50 mg/ml Injection (Pfizer Limited). Consequently, the Patient Information Leaflet (PIL) has been updated.

Supporting Evidence
Revised SmPC fragments (sections) and an amended leaflet have been provided.

No new additional data was submitted or required.

Evaluation
The proposed changes are consistent with those in the current product information (SmPC sections 4.2, 4.6 and 5.2 and PIL section 2) of the reference product Ketalar 50 mg/ml Injection (PL 00057/0530; Pfizer Limited) regarding use and pharmacokinetics in the obstetric patient, which was last updated on 12th January 2016. The mockup now contains the updated information and retains the previously approved house style.

Conclusion
The updated sections of the SmPC and the leaflet are acceptable and there are no objections to approval.

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

Decision - Approved on 18 March 2016