IPAR

Public Assessment Report for a
Medicinal Product for Human Use

Scientific Discussion

Oxycodone Hydrochloride 10 mg/ml Solution for Injection or Infusion
OXYCODONE HYDROCHLORIDE
PA0281/235/001

The Public Assessment Report reflects the scientific conclusion reached by the Health Products Regulatory Authority (HPRA) at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation for a specific medicinal product for human use. It is made available by the HPRA for information to the public, after deletion of commercially sensitive information. The legal basis for its creation and availability is contained in Article 21 of Directive 2001/83/EC, as amended. It is a concise document which highlights the main parts of the documentation submitted by the applicant and the scientific evaluation carried out by the HPRA leading to the approval of the medicinal product for marketing in Ireland.

CONTENTS

I. INTRODUCTION

This product was initially authorised under procedure number UK/H/2915/1/DC with the UK as RMS. The responsibility of RMS was transferred to Ireland on 25/01/2019 under procedure number IE/H/0937/1/DC
Please note the following detail for the product in IE:
Marketing Authorisation Number: PA0281/235/001
Marketing Authorisation Holder: Pinewood Laboratories Ltd

The current Summary of Product Characteristics (SmPC) for this medicinal product is available on the HPRA website at www.hpra.ie.

The UK public assessment report published at the time of the initial marketing authorisation is provided herein.

Based on the review of the data on quality, safety and efficacy, the MHRA granted Wockhardt UK Limited a Marketing Authorisation for the medicinal product Oxycodone Hydrochloride 10 mg/ml Solution for Injection or Infusion (PL 29831/0359, UK/H/2915/001/DC) on 7th May 2010. The product is a prescription-only medicine.

This is an abridged application for Oxycodone Hydrochloride 10 mg/ml Solution for Injection or Infusion, submitted under Article 10.1 of 2001/83 EC, as amended. The application refers to OxyNorm® 10mg/ml solution for injection or infusion (PL 16950/0128), authorised to Napp Pharmaceuticals Limited in the UK on 14th April 2003. Napp Pharmaceuticals Limited holds a licence for Oxycontin® 10mg prolonged-release tablets, for the same active substance, granted in Ireland on 28th May 1998. The EU originator product, Oxycontin® 10mg prolonged-release tablets, has been authorised in the EEA for more than 10 years, so the period of data exclusivity has expired. With the UK as the Reference Member State in this Decentralised Procedure, Wockhardt UK Limited applied for a Marketing Authorisation for Oxycodone Hydrochloride 10 mg/ml Solution for Injection or Infusion in Cyprus, Ireland, Malta and Poland.

Oxycodone Hydrochloride 10 mg/ml Solution for Injection or Infusion is indicated for the treatment of moderate to severe pain in patients with cancer and post-operative pain; and for the treatment of severe pain requiring the use of a strong opioid.

Oxycodone belongs to the pharmacotherapeutic group, natural opium alkaloids (ATC code - N02A A05). Oxycodone is a full opioid agonist with no antagonist properties. It has an affinity for kappa, mu and delta opioid receptors in the brain and spinal cord. Oxycodone is similar to morphine in its action. The therapeutic effect is mainly analgesic, anxiolytic, antitussive and sedative. Opioids may influence the hypothalamic-pituitary-adrenal or gonadal axes. Some changes that can be seen include an increase in serum prolactin and decreases in plasma cortisol and testosterone. Clinical symptoms may be manifest from these hormonal changes.

Pharmacokinetic studies in healthy subjects demonstrated an equivalent availability of oxycodone from oxycodone injection when administered by the intravenous and subcutaneous routes, as a single bolus dose or a continuous infusion over 8 hours. Following absorption, oxycodone is distributed throughout the entire body. Approximately 45% is bound to plasma protein. It is metabolised in the liver to produce noroxycodone, oxymorphone and various conjugated glucuronides. The analgesic effects of the metabolites are clinically insignificant. The active drug and its metabolites are excreted in both urine and faeces.

The medicinal product is presented as a clear, colourless solution for injection or infusion. It must not be mixed with other medicinal products except those mentioned in section 6.6 of the SmPC. This medicine is not for self-administration; it will be administered to the patient by a healthcare professional.

No new pre-clinical or clinical studies were conducted, which is acceptable given that this is a generic application cross-referring to a product that has been licensed for over 10 years. Bioequivalence studies are not necessary to support this application for a parenteral product.

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 and assembly of this product. Evidence of compliance with GMP has been provided for the named manufacturing and assembly sites. 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 considers that the pharmacovigilance system as described by the MAH fulfils the requirements and provides adequate evidence that the MAH has 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.

The Marketing Authorisation Holder has provided adequate justification for not submitting an Environmental Risk Assessment (ERA). This was an application for a generic product and there is no reason to conclude that marketing of this product will change the overall use pattern of the existing market. The Marketing Authorisation Holder has provided adequate justification for not submitting a Risk Management Plan (RMP). As the application is for a generic version of an already authorised reference product, for which safety concerns requiring additional risk minimisation have not been identified, a risk minimisation system is not considered necessary. The reference product has been in use for many years and the safety profile of the active is well established.

II. QUALITY ASPECTS

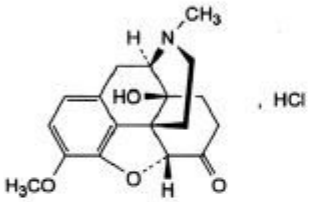
ACTIVE SUBSTANCE

Oxycodone hydrochloride

Nomenclature:

INN:	Oxycodone hydrochloride
Chemical names:	4,5a-Epoxy-14-hydroxy-3-methoxy-17-methylmorphinan-6-one hydrochloride

Structure:



, HCl

Molecular formula:	$C_{18}H_{22}ClNO_4$, HCl
Molecular weight:	351.9 g/mol
CAS No:	124-90-3
Physical form:	White or almost white powder, hygroscopic
Solubility:	Freely soluble in water, sparingly soluble in anhydrous ethanol, practically insoluble in toluene

The active substance, oxycodone hydrochloride, is the subject of a European Pharmacopoeia (Ph. Eur.) monograph.

All aspects of the manufacture and control of oxycodone hydrochloride are supported by an EDQM Certificate of Suitability (CEP). This certificate is accepted as confirmation of the suitability of oxycodone hydrochloride for inclusion in this medicinal product.

The current CEP states a re-test period of 5 years for the active substance.

MEDICINAL PRODUCT

Other ingredients

The finished product is presented as a clear, colourless, sterile solution of oxycodone hydrochloride in water for injections. Each 1ml dose contains 10mg oxycodone hydrochloride, equivalent to 9mg/ml oxycodone base.

Other ingredients consist of pharmaceutical excipients, namely citric acid monohydrate, sodium citrate, sodium chloride, sodium hydroxide (for pH adjustment), hydrochloric acid (for pH adjustment), and water for injections. Appropriate justification for the inclusion of each excipient has been provided.

All excipients used comply with their respective European Pharmacopoeia monographs, with the exception of sodium hydroxide and hydrochloric acid, which comply with satisfactory in-house specifications. Satisfactory Certificates of Analysis have been provided for all excipients.

The applicant has provided a declaration confirming that there are no materials of human or animal origin contained in or used in the manufacturing process for the proposed product.

There were no novel excipients used and no overages.

Pharmaceutical development

Details of the pharmaceutical development of the drug product have been supplied and are satisfactory. The objective was to develop a stable formulation for oxycodone hydrochloride 10mg/ml solution for injection or infusion, in 1ml and 2ml glass ampoules, with similar physical and chemical characteristics to the comparator product Oxynorm® 10mg/ml solution for injection or infusion supplied by Napp Pharmaceuticals Ltd.

Manufacture

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

In-process controls are appropriate considering the nature of the product and the method of manufacture. Satisfactory process validation data were provided and all data were within specification.

Finished product specification

The finished product specifications are provided for both release and shelf life and are satisfactory; they provide an assurance of the quality and consistency of the finished product. Acceptance limits have been justified with respect to conventional pharmaceutical requirements and, where appropriate, safety. Test methods have been described and have been adequately validated, as appropriate. Satisfactory batch analysis data are provided for two batches of the finished product, presented in both 1ml and 2ml ampoules. The data demonstrate that the batches are compliant with the proposed specifications. Certificates of Analysis have been provided for any reference standards used.

Container Closure System

The finished product is licensed for marketing in clear, colourless Type I glass ampoules of volume 1ml or 2ml. The ampoules contain 1ml or 2ml of sterile solution of oxycodone hydrochloride (concentration 10 mg/ml).

The ampoules are packaged with the Product Information Leaflet (PIL) into cardboard outer cartons, in pack sizes of 5. The ampoules satisfy Directive 2002/72/EC (as amended), and are suitable for contact with parenteral preparations. Specifications and Certificates of Analysis for all packaging components used have been provided, and are satisfactory.

Stability

Finished product stability studies have been conducted in accordance with current guidelines and results were within the proposed specification limits. Based on the results, a shelf-life of 2 years has been set for the unopened ampoule, which is satisfactory. The injection should be given immediately after opening the ampoule. This medicinal product does not require any special storage conditions. For further advice for use of the opened ampoule, refer to section 6.3 of the SmPC. Please also refer to the SmPC for information on compatible or incompatible products, and handling of this product.

Bioequivalence Study

Bioequivalence studies are not necessary to support this application for a parenteral product.

Quality Overall Summary

A satisfactory quality overview is provided, and has been prepared by an appropriately qualified expert. The CV of the expert has been supplied.

Product Information

The approved SmPC, and labelling and leaflet texts are satisfactory. The MAH has committed to submitting mock-ups for the packaging and PIL for assessment before packs are commercially marketed.

Conclusion

The proposed product, Oxycodone Hydrochloride 10 mg/ml Solution for Injection or Infusion, has been shown to be a generic version of the reference product, OxyNorm® 10mg/ml solution for injection or infusion (PL 16950/0128, Napp Pharmaceuticals Limited), with respect to qualitative and quantitative content of the active substance, and the pharmaceutical form. The test product is pharmaceutically equivalent to the reference product, and the originator product, Oxycontin® 10mg prolonged-release tablets, has been licensed in the UK for over 10 years. Given the route of administration and pharmaceutical form, it is not necessary to demonstrate bioequivalence of the proposed product to the reference product.

All pharmaceutical issues have been resolved and the quality grounds for this application are considered adequate. A Marketing Authorisation has therefore been granted.

III. NON-CLINICAL ASPECTS

III.2 NON-CLINICAL ASPECTS

Specific non-clinical studies have not been performed, which is acceptable for this application for a generic version of a product that has been licensed for over 10 years. The non-clinical overview provides a satisfactory review of the pharmacodynamic, pharmacokinetic, and toxicological properties of oxycodone hydrochloride, which is a widely used and well-known active substance. The CV of the non-clinical expert has been supplied. For generic applications of this nature, the need for repetitive tests on animals and humans is avoided. Reference is made to the reference medicinal product, OxyNorm® 10mg/ml solution for injection or infusion (Napp Pharmaceuticals Limited).

IV. CLINICAL ASPECTS

III.3 CLINICAL ASPECTS

INDICATIONS

Oxycodone Hydrochloride 10 mg/ml Solution for Injection or Infusion is indicated for the treatment of moderate to severe pain in patients with cancer and post-operative pain; and for the treatment of severe pain requiring the use of a strong opioid.

The indications are consistent with those for the reference product and are satisfactory.

POSOLOGY AND METHOD OF ADMINISTRATION

Full details concerning the posology are provided in the SmPC. The posology is consistent with that for the reference product and is satisfactory.

TOXICOLOGY

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

CLINICAL PHARMACOLOGY

The clinical pharmacology of oxycodone hydrochloride is well known. No novel pharmacodynamic or pharmacokinetic data are supplied or required for this application.

Clinical efficacy

No new data are submitted and none are required for this type of application. Efficacy is reviewed in the clinical overview. The efficacy of oxycodone hydrochloride is well-established from its extensive use in clinical practice.

Oxycodone Hydrochloride 10 mg/ml Solution for Injection or Infusion is to be administered as an aqueous intravenous solution and contains the same active substance, in the same concentration, as the currently authorised reference product, OxyNorm® 10mg/ml solution for injection or infusion (PL 16950/0128, Napp Pharmaceuticals Limited). Thus, in accordance with the "Note for Guidance on the Investigation of Bioavailability and Bioequivalence", (CPMP/EWP/QWP/1401/98), the applicant is not required to submit a bioequivalence study.

Clinical safety

No novel safety data have been submitted and none are required for applications of this type. The safety profile of oxycodone hydrochloride is well-known. No new or unexpected safety concerns arose from this application. Safety is reviewed in the clinical overview.

PRODUCT INFORMATION:

Summary of Product Characteristics (SmPC)

The approved SmPC is consistent with that for the reference product, and is acceptable.

Product Information Leaflet (PIL)

The final PIL text is in line with the approved SmPC and is satisfactory.

Labelling

The labelling text is satisfactory.

Expert Report

A satisfactory clinical overview is provided, and has been prepared by an appropriately qualified expert. The CV of the expert has been supplied.

Post marketing experience

No post-marketing data are available. The medicinal product has not been marketed in any country. Oxycodone has a well-recognised efficacy and an acceptable level of safety in the approved indications.

CONCLUSIONS & DISCUSSION

The grounds for establishing the proposed product, Oxycodone Hydrochloride 10 mg/ml Solution for Injection or Infusion, as a generic version of the reference product, OxyNorm® 10mg/ml solution for injection or infusion (PL 16950/0128, Napp Pharmaceuticals Limited), are considered adequate. The product literature is approved.

Sufficient clinical information has been submitted to support this application. All issues have been adequately addressed by the applicant. When used as indicated, Oxycodone Hydrochloride 10 mg/ml Solution for Injection or Infusion has a favourable benefit-to-risk ratio. The granting of a Marketing Authorisation was therefore recommended on clinical grounds.

V. OVERALL CONCLUSIONS

IV OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

QUALITY

The important quality characteristics of Oxycodone Hydrochloride 10 mg/ml Solution for Injection or Infusion 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.

EFFICACY

The applicant's Oxycodone Hydrochloride 10 mg/ml Solution for Injection or Infusion has been demonstrated to be a generic version of the reference product, OxyNorm® 10mg/ml solution for injection or infusion (PL 16950/0128, Napp Pharmaceuticals Limited).

No new or unexpected safety concerns arise from this application.

PRODUCT LITERATURE

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

The leaflet text 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 results show that the leaflet text 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.

The Marketing Authorisation Holder (MAH) has committed to submitting mock-ups for the packaging and PIL for assessment before packs are commercially marketed.

RISK BENEFIT ASSESSMENT

The quality of the product is acceptable and no new non-clinical or clinical safety concerns have been identified. The qualitative and quantitative assessment supports the claim that the applicant's Oxycodone Hydrochloride 10 mg/ml Solution for Injection or Infusion and the reference product, OxyNorm® 10mg/ml solution for injection or infusion (Napp Pharmaceuticals Limited), are interchangeable. Extensive clinical experience with oxycodone hydrochloride is considered to have demonstrated the therapeutic value of the active substance. The risk: benefit ratio is considered to be positive.

VI. REVISION DATE

22/02/2022

VII. UPDATES

This section reflects the significant changes following finalisation of the initial procedure.

SCOPE	PROCEDURE NUMBER	PRODUCT INFORMATION AFFECTED	DATE OF START OF PROCEDURE	DATE OF END OF PROCEDURE
RMS transfer	From UK/H/2915/1/DC to IE/H/0937/1/DC			