Public Assessment Report

Decentralised Procedure

Oxycodone Hydrochloride 50 mg/ml Solution for Injection or Infusion

Procedure No: UK/H/5246/001/DC

UK Licence No: PL 29831/0367

Wockhardt UK Limited
LAY SUMMARY

On 04 July 2013, the Medicines and Healthcare products Regulatory Agency (MHRA) granted a Marketing Authorisation to Wockhardt UK Limited for the medicinal product Oxycodone Hydrochloride 50 mg/ml Solution for Injection or Infusion (PL 29831/0367; UK/H/5246/001/DC). This is a prescription-only medicine (POM) used to relieve moderate to severe pain.

Oxycodone Hydrochloride 50 mg/ml Solution for Injection or Infusion contains the active ingredient oxycodone (as oxycodone hydrochloride), which belongs to a group of medicines called strong analgesics or ‘painkillers’.

No new or unexpected safety concerns arose from this application and it was therefore judged that the benefits of taking Oxycodone Hydrochloride 50 mg/ml Solution for Injection or Infusion outweigh the risks and a Marketing Authorisation was granted.
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Module 1
Information about the initial procedure

<table>
<thead>
<tr>
<th>Product Name(s)</th>
<th>Oxycodone Hydrochloride 50mg/ml for Injection or Infusion</th>
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<tbody>
<tr>
<td>Type of Application</td>
<td>Generic, Article 10(1)</td>
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<td>Active Substance(s)</td>
<td>Oxycodone hydrochloride</td>
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<tr>
<td>Form</td>
<td>Solution for injection or infusion</td>
</tr>
<tr>
<td>Strength</td>
<td>50 mg/ml</td>
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</table>
| MA Holder | Wockhardt UK Limited  
Ash Road North  
Wrexham  
LL13 9UF  
UK |
| Reference Member State (RMS) | UK |
| Concerned Member States (CMS) | Ireland |
| Procedure Number(s) | UK/H/5246/001/DC |
| Timetable | Day 210 – 20 June 2013 |
Module 2
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.
Module 3
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.
Module 4
Labelling

**Oxycodone Hydrochloride 50 mg/ml Solution for Injection or Infusion**

**Caution:** The contents of each ampoule exceed the usual starting dose. Please check the ampoule label carefully for subcutaneous or intravenous use.

5 ampoules
Module 5
Scientific discussion during initial procedure

I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the UK and Ireland considered that the application for Oxycodone Hydrochloride 50 mg/ml Solution for Injection or Infusion (PL 29831/0367; UK/H/5246/001/DC) could be approved. The product is a prescription-only medicine (POM).

The application was submitted using the Decentralised Procedure (DCP), with the UK as Reference Member State (RMS) and Ireland as Concerned Member State (CMS). The application was submitted under Article 10(1) of Directive 2001/83/EC, as amended, claiming to be a generic medicinal product of OxyNorm 50mg/ml solution for injection or infusion (PL 16950/0155; Napp Pharmaceuticals Limited, UK) which was authorised in the UK on 14 January 2009. The reference product authorised in the Community for more than 10 years is OxyContin 40 mg Prolonged Release Tablets authorised to Napp Pharmaceuticals Ltd in the Republic of Ireland.

The active ingredient, oxycodone (as oxycodone hydrochloride), 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 product is indicated for the treatment of moderate to severe pain in patients with cancer and post-operative pain. It is also indicated for the treatment of severe pain requiring the use of a strong opioid.

No new non-clinical or clinical studies were performed, which is acceptable given that the application was based on the product being a generic medicinal product of an originator product that has been in clinical use for over 10 years. A bioequivalence study was not necessary to support this application for a parenteral product (aqueous solution).

The RMS has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place 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 (Day 210) on 20 June 2013. After a subsequent national phase, a licence was granted in the UK on 04 July 2013.
II. ABOUT THE PRODUCT

| Name of the product in the Reference Member State | Oxycodone Hydrochloride 50mg/ml for Injection or Infusion |
| Name(s) of the active substance(s) (INN) | Oxycodone hydrochloride |
| Pharmacotherapeutic classification (ATC code) | Natural opium alkaloids (ATC code: N02A A05) |
| Pharmaceutical form and strength(s) | Solution for injection or infusion |
| Reference number for the Decentralised Procedure | UK/H/5246/001/DC |
| Reference Member State (RMS) | United Kingdom |
| Concerned Member States (CMS) | Ireland |
| Marketing Authorisation Numbers | PL 29831/0367 |
| Name and address of the authorisation holder | Wockhardt UK Limited Ash Road North Wrexham LL13 9UF UK |

III. SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 QUALITY ASPECTS

ACTIVE SUBSTANCE

INN: Oxycodone hydrochloride
Compendial Name: Oxycodone hydrochloride (European Pharmacopoeia)
Chemical Name: 4,5a-Epoxy-14-hydroxy-3-methoxy-17-methylmorphinan-6-one hydrochloride
Molecular formula: C$_{18}$H$_{22}$ClNO$_{4}$
Structure:

Oxycodone hydrochloride is the subject of a European Pharmacopoeia monograph.

Molecular mass: 351.9
Appearance: White or almost white powder, hygroscopic
Solubility: Freely soluble in water, sparingly soluble in anhydrous ethanol, practically insoluble in toluene.

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

MEDICINAL PRODUCT

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

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

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.

**Pharmaceutical Development**

The objective of the development programme was to produce a stable formulation of oxycodone hydrochloride in a 50 mg/ml solution for injection or infusion comparable in performance to the reference product OxyNorm 50mg/ml solution for injection or infusion (Napp Pharmaceuticals Ltd, UK).

Suitable pharmaceutical development data have been provided for this application.

Comparative impurity profiles have been provided for this product and the reference 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 full production-scale batches that have shown satisfactory results.

**Control of Finished Product**

The finished product specification is acceptable. Test methods have been described that have been suitably validated. Batch data have been provided, which comply with the release specifications. Certificates of Analysis have been provided for all working standards used.

**Container-Closure System**

The finished product is supplied in 1 ml Type I clear, neutral glass ampoules, packed in cardboard outer cartons in pack sizes of 5 ampoules.

Satisfactory specifications and Certificates of Analysis for the primary packaging material have been provided. All primary packaging is controlled to European Pharmacopoeia standards and complies with guidance concerning materials in contact with parenteral products.

**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 2 years has been approved for the unopened product, with the storage conditions “Do not store above 25°C. Keep the ampoule in the outer carton in order to protect from light.”

The injection should be given immediately after opening the ampoule. Once opened, any unused portion should be discarded.

If not used immediately, it is stated that in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8°C.

**Bioequivalence/Bioavailability**

A bioequivalence study was not necessary to support this application for this aqueous solution, parenteral product.
**Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labels**

The SmPC, PIL and labels are satisfactory from a pharmaceutical perspective.

User testing of the package leaflet for Oxycodone Hydrochloride 50mg/ml Solution for Injection or Infusion (PL 29831/0367) has been accepted based on a bridging report provided by the applicant making reference to the satisfactory user-testing of the PIL for Oxycodone Hydrochloride 10 mg/ml Solution for Injection or Infusion (PL 29831/0359), as the ‘parent PIL’.

**Marketing Authorisation Application (MAA) Form**

The MAA form is satisfactory from a pharmaceutical perspective.

**Expert Report (Quality Overall Summary)**

The quality overall summary has been 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.

**III.2 NON-CLINICAL ASPECTS**

As the pharmacodynamic, pharmacokinetic and toxicological properties of oxycodone hydrochloride are well-known, no new non-clinical data have been submitted and none are required.

The applicant’s 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.

Suitable justification has been provided for non-submission of an Environmental Risk Assessment. As this product is intended for generic substitution with a product that is already marketed, no increase in environmental burden is anticipated. Thus, the justification for non-submission of an Environmental Risk Assessment is accepted.

The grant of a Marketing Authorisation is recommended.

**III.3 CLINICAL ASPECTS**

**Clinical Pharmacology**

No new clinical pharmacology data have been submitted and none are required for applications of this type. 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 (CPMP/EWP/QWP/1401/98 Rev. 1/Corr** (Guideline on the Investigation of Bioequivalence).

**Efficacy**

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

**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. As an active ingredient, oxycodone hydrochloride has a well-established safety profile and an acceptable level of safety in the proposed indications.
Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labels
The SmPC, PIL and labels are acceptable from a clinical perspective. The SmPC is consistent with that for the innovator product. The PIL is consistent with the details in the SmPC and in line with the current guidance. The labelling is in line with the current guidance.

Clinical Expert Report (Clinical Overview)
The clinical overview has been written by an appropriately qualified physician and is a suitable summary of the clinical aspects of the dossier.

Pharmacovigilance System and Risk Management Plan
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.

A suitable justification has been provided for not submitting a Risk Management Plan for this application.

Conclusion
The grant of a Marketing Authorisation is recommended.

IV OVERALL CONCLUSION AND BENEFIT/RISK ASSESSMENT
QUALITY
The important quality characteristics of Oxycodone Hydrochloride 50 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 this type of application.

EFFICACY
No new clinical data were submitted for this application. No bioequivalence studies were submitted or required for this application.

SAFETY
No new or unexpected safety concerns arise from this application.

PRODUCT LITERATURE
The SmPC, PIL and labelling are satisfactory and consistent with those for the reference product, where appropriate and in line with current guidance.

BENEFIT/RISK ASSESSMENT
The quality of the products is acceptable, and no new non-clinical or clinical safety concerns have been identified. The data supplied supports the claim that the applicant’s product and the reference product are interchangeable. Extensive clinical experience with oxycodone hydrochloride is considered to have demonstrated the therapeutic value of the compound. The benefit/risk balance is therefore considered to be positive.
Module 6

STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

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<th>Application type</th>
<th>Scope</th>
<th>Outcome</th>
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