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IRISH MEDICINES BOARD

PUBLIC ASSESSMENT REPORT FOR A MEDICINAL PRODUCT FOR HUMAN USE

Scientific discussion

OxyNorm 50 mg/ml Solution for Injection or Infusion

OXYCODONE HYDROCHLORIDE

PA 1688/6/10

The Public Assessment Report reflects the scientific conclusion reached by the Irish Medicines Board (IMB) 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 IMB 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 IMB leading to the approval of the medicinal product for marketing in Ireland.

I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the IMB has granted a marketing authorisation for OxyNorm 50 mg/ml Solution for Injection or Infusion, from Napp Pharmaceuticals Limited on 2nd September 2011 for the treatment of severe pain.

This application for a marketing authorisation was submitted in accordance with Regulation (EC) 1084/2003 based on a change (new strength) to the existing marketing authorisation OxyNorm 10 mg/ml Solution for Injection or Infusion.

The Summary of Product Characteristics for (SPC) for this medicinal product is available on the IMB's website at www.imb.ie

Name of the product	OxyNorm 50 mg/ml Solution for Injection or Infusion
Name(s) of the active substance(s) (INN)	OXYCODONE HYDROCHLORIDE
Pharmacotherapeutic classification (ATC code)	N02AA05
Pharmaceutical form and strength(s)	50 mg/ml Solution for Injection or Infusion
Marketing Authorisation Number(s) in Ireland (PA)	PA 1688/006/010
Marketing Authorisation Holder	Mudipharma Pharmaceuticals Limited

II QUALITY ASPECTS

II.1. Introduction

This application for OxyNorm 50mg/ml Solution for Injection or Infusion is submitted in accordance with Directive 2001/83/EC Article 8 (3) for a line extension of OxyNorm 10mg/ml Solution for Injection or Infusion held by the applicant. The national authorisation was granted on 2nd September 2011. The product is a solution for injection/infusion consisting of the commonly used and well known active substance Oxycodone hydrochloride.

II.2 Drug substance

The drug substance is Oxycodone Hydrochloride, an established drug substance described in the European Pharmacopoeia (Ph. Eur.), which is manufactured in accordance with Good Manufacturing Practice (GMP). The EDQM/Ph. Eur. CEP procedure is used for the active substance.

The active substance specification is considered adequate to control the quality and meets the current requirements of the monograph in the Ph. Eur. Batch analytical data demonstrating compliance with this specification have been provided for three representative batches.

The EDQM has approved a re-test period of five years.

II.3 Medicinal product

P.1 Composition

The product is a preservative free, clear, colourless to pale yellow, sterile solution for injection or infusion in Water for Injection with a pH adjuster and buffering agents. The solution is made isotonic using sodium chloride. The solution is filled into type I Ph. Eur. neutral, colourless 1ml ampoules in a cardboard box.

The drug substance is Oxycodone hydrochloride. Each ml contains 50 mg of Oxycodone hydrochloride. The excipients are: Sodium Citrate, Citric Acid, Sodium hydroxide, Hydrochloric Acid, Sodium chloride and Water for Injections.

P.2 Pharmaceutical Development

The drug product is a solution for injection or infusion containing 50 mg/ml of oxycodone hydrochloride. The product is intended for subcutaneous or intravenous administration to patients who require relief from severe pain.

The aim of the development was to formulate a stable aqueous injection for parenteral use containing 50 mg/ml of oxycodone hydrochloride to complement the existing Oxynorm 10 mg/ml Solution for Injection or Infusion and range of oral oxycodone products - prolonged release tablets, immediate release capsules and liquids which are currently marketed by the MAH in a number of European countries. The product development is adequately described in accordance with the relevant European guidelines.

P.3 Manufacture of the Product

The product is manufactured in accordance with the principles of good manufacturing practice (GMP). The product is manufactured using conventional manufacturing techniques. The manufacturing process is considered adequately validated according to relevant European/ICH guidelines.

P.4 Control of Other Substances (Excipients/*Ancillary Substances)*

All excipients comply with their respective European Pharmacopoeia monographs. There are no excipients of human or animal origin used in the manufacture of the product. There are no novel excipients used in the manufacture of the product.

P.5 Control of Finished Product

The finished product specification is adequate to control the relevant parameters for the dosage form. The release specifications for the drug product are based on the Ph. Eur. monograph for Oxycodone Hydrochloride and the standard requirements associated with parenteral preparations. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. Satisfactory validation data for analytical methods have been provided. Batch analytical data from the proposed production site have been provided demonstrating compliance with the specification.

P.6 Packaging material

The product is presented in glass ampoules, made of neutral glass, type I with a fill volume of 1ml according to Ph. Eur. process. The ampoules are placed in a cardboard box. Ampoule drawings and test certificates are provided. The ampoules comply with the requirements of Ph. Eur.

P.7 Stability of the Finished Product

Stability data on the finished product in the proposed packaging have been provided in accordance with EU guidelines demonstrating the stability of the product.

The approved shelf life of the product as packaged for sale and the storage conditions are stated in the Summary of Product Characteristics (SPC). Once open the product should be used immediately (see the SPC for further information).The product as package for sale does not require any special temperature storage precautions prior to use, but the ampoules should be kept in the outer carton in order to protect them from light. The product can be administrated either as injection or infusion and therefore compatibility of the product has been assessed and demonstrated with range of materials and common diluents. All compatibilities and incompatibilities are adequately documented in relevant sections of the SPC.

II.4 Discussion on Chemical, Pharmaceutical and Biological Aspects

The important quality characteristics of the product are well-defined and controlled. Satisfactory chemical and pharmaceutical documentation has been provided, assuring consistent quality of OxyNorm 50 mg/ml Solution for Injection or Infusion.

III NON-CLINICAL ASPECTS

III.1 Introduction

OxyNorm 50 mg/ml Solution for Injection or Infusion is a liquid formulation containing the active ingredient oxycodone hydrochloride. As a single drug substance, oxycodone has been available for administration as an oral solution (1 mg/ml and 10 mg/ml), a prolonged release tablet (5 mg, 10 mg, 20 mg, 40 mg, 80 mg, 160 mg) an IR capsule (5 mg, 10 mg, 20 mg) and a 10 mg/ml parenteral formulation.
The safety profile and efficacy of oxycodone hydrochloride have been well established in clinical use, in humans, in a large number of countries since its inception approximately eighty years ago. Oxycodone is a full opioid agonist with no antagonist properties. It has an affinity for kappa, mu and delta opiate receptors in the brain and spinal cord. The therapeutic effect is mainly analgesic, anxiolytic and sedative.

III.2 Pharmacology

The pharmacology of Oxycodone has been extensively studied *in vivo* and has consistently demonstrated activity in rodent models of acute nociceptive pain. An extensive review of the literature surmises that, in terms of general pharmacology, the qualitative profile of oxycodone appears to be the same as that of morphine and other similar opioid analgesics in both the pre-clinical and clinical setting. Oxycodone appears to be more potent than morphine in its CNS and respiratory effects, In terms of gastrointestinal functioning, oxycodone is qualitatively similar to morphine; however, it appears to be less potent than morphine in several tests, such as inducing emesis in dogs, inhibition of propulsion of a charcoal meal and inhibition of ricinus oil induced diarrhoea. The general pharmacological activities of the two drugs on the cardiovascular system and renal functions appear to be similar.
The applicant performed two further studies which confirmed the antinoceptive effects of Oxycodone and demonstrated that both younger and old rats were equally sensitive to Oxycodone, with weight not appearing to be a factor. The applicant also demonstrated that oxycodone has no clinically significant inhibitory effect on the hERG channel, which is involved in the repolarisation of cardiac myocytes and is considered an important component of the evaluation of cardiac safety.

III.3 Pharmacokinetics

No new studies were performed with respect to pharmacokinetics as a considerable amount of preclinical toxicology and pharmacokinetics/ADME already exists for
oxycodone. Its absorption, metabolic and excretion profiles in nonclinical species are similar to those in humans. Oxycodone is rapidly absorbed and metabolised and noroxycodone is the major circulating metabolite in all species. CYP2D6 and CYP3A4 isoforms were involved in oxycodone metabolism in human and non-human species. Enzyme inhibition studies indicated that oxycodone did not inhibit the major P450 metabolizing enzymes and therefore, few if any drug interactions would be expected with other co-administered drugs metabolized by most CYP isoforms, with the exception of ketoconazole, a known potent CYP3A4 inhibitor. In addition, unlike morphine, oxycodone was not found to be a P-gp substrate and consequently will not interact at the blood-brain barrier with concomitantly administered P-gp substrates.

III.4 Toxicology

The toxicology of oxycodone has been previously reviewed within the literature and oxycodone has been used clinically in several European countries including France, Germany and the United Kingdom for a number of years. There is considered to be extensive clinical data and it is considered that the safety profile has been well established.

Based on published data, together with company studies (acute and repeated dose toxicology studies (through 3-months) as well as genotoxicity studies, it is concluded that oxycodone has a similar side effect and toxicity profile to that of morphine and other opioid analgesics. The primary drug-related findings are present as clinical/pharmacotoxic signs. No clear drug-related histopathological effects have been found despite very high plasma concentrations and

AUC values along with severe signs of intoxication.

A series of new studies were performed in order to assess the potential local toxicity as well as toxicokinetics following administration via the proposed route of administration with the new formulations. There were considered to be no significant findings with respect to local toxicity following single or repeat dosing using the 10 mg/ml formulation, with the exception of reactions following single intramuscular injection in the rat.

These reactions were considered to be due to the volume rather than the dose of oxycodone hydrochloride, which is considered acceptable.

Single and repeat dose studies with 25 and 50 mg/ ml were noted to be without irritation potential following 24 hour continuous intravenous or subcutaneous infusion. Some irritation was noted following 96 hours of continuous infusion with slightly more severe signs of irritation following 14 days continuous infusion. The mg / kg doses used in these studies were approximately 7.5-100 times (bolus dosing) and 17-120 times (infusions) the mg / kg starting doses in humans. Based on the data the proposed 10 and 50 mg/ml solutions for injection are considered to represent a slight irritation potential, however the clinical section there are no reports of injection site reactions with the exception of one report of injection site pain.
The only toxicity finding of note was that at mid and high doses administered intramuscularly, there was no further increase in exposure and, local inflammatory reactions were observed. It is considered that these reactions are due to the volume administered rather than the dose of oxycodone hydrochloride. Overall there are considered to be no new concerns with respect to the systemic and local safety and tolerance of oxycodone hydrochloride and the proposed volume to be administered to humans is considered acceptable

Reproductive toxicity studies indicate that oxycodone does not adversely affect fertility of rats or rabbits, even at maternally toxic doses. Oxycodone does not affect reproductive performance in rats dosed during gestation and lactation; does not affect long-term development or reproductive performance in pups (F_1 generation) born to rats treated with oxycodone during late pregnancy and lactation and does not have developmental effects on rats born to the F_1 generation female. Published literature (Marx et al., 1986) has demonstrated that oxycodone is secreted in human breast milk. The SmPC therefore states that oxycodone should not be used by breast-feeding mothers.

III.5 Ecotoxicity/environmental risk assessment

The company performed a Phase I , Evironmental Exposure Assessment in accordance with the Guidance on the Environmental Risk Assessment of Medical Products for Human Use (EMEA/CHMP/SWP/4447/00) Based on the results of this assessment it is concluded that based on the proposed use oxycodone is unlikely to represent a risk to the environment and no further action is required.

III.6 Discussion on the non-clinical aspects

The safety profile and efficacy of oxycodone hydrochloride have been well established in clinical use, in humans, in a large number of countries since its inception approximately eighty years ago. The new product will not increase the level of exposure to oxycodone and therefore the previous clinical experience is considered to be relevant. New studies were performed with respect to the local toxicity and toxicokinetics. Observed, local toxicity effects were related to the volume administered rather than the active substance and are not considered relative to the clinical situation.
Signs of irritation were observed in some animal studies however this potential for irriation is not reflected in the clinical situation.

IV CLINICAL ASPECTS

IV.1 Introduction

Oxycodone hydrochloride is a well known active substance with established efficacy and tolerability.

This application for a marketing authorisation was submitted in accordance with Regulation (EC) 1084/2003 based on a change (new strength) to the existing marketing authorisation OxyNorm 10 mg/ml Solution for Injection or Infusion. This is a so called ‘line extension’ and does not require the conduct of new clinical studies.

The Marketing Authorisation Holder submitted a set of documents describing the Pharmacovigilance System, including information on the availability of an EU Qualified Person for Pharmacovigilance (EU-QPPV) and the means for notification of adverse reaction reports in the EU or from a Third Country.

IV.6 Discussion on the clinical aspects

The application is based on an extension to the existing marketing authorisation for OxyNorm 10 mg/mL Solution for Injection or Infusion and is based on the clinical experience of safety and efficacy with that product since 1993, and more generally with the active substance oxycodone hydrochloride over more than fifty years of therapeutic use. The purpose of introducing a more concentrated formulation is that patients treated over a protracted period (months) with oxycodone develop tolerance and require increasing doses to achieve pain relief. Ultimately they may require very large doses and the concentrated form of 50 mg/mL facilitates adminstration.

V OVERALL CONCLUSIONS

Benefit/Risk Assessment and Recommendation

Oxycodone hydrochloride is a well known active substance with established efficacy and tolerability; it has been in therapeutic use for more than fifty years.

The application for a marketing authorisation is in accordance with Regulation (EC) 1084/2003 based on a change (new strength) to the existing marketing authorisation OxyNorm 10 mg/ml Solution for Injection or Infusion and does not require the conduct of new clinical studies. The purpose of introducing a more concentrated formulation is to facilitate administration to patients requiring high doses of parenteral oxycodone.

The OxyNorm 50 mg/mL has been in clinical use in several countries worldwide since 2008. The risk benefit of the product is considered positive.