IPAR

Public Assessment Report for a
Medicinal Product for Human Use

Scientific Discussion

OxyNorm 10 mg/ml, solution for injection or infusion
OXYCODONE HYDROCHLORIDE
PA1688/006/001

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

The application is for a parenteral formulation (10mg/ml) of the well known opioid agonist oxycodone hydrochloride which has had wide use in clinical practice many years. The Applicant markets a range of oxycodone-containing products for oral administration (OxyContin® tablets and OxyNorm® capsules, liquid, and concentrate). OxyNorm 10 mg/ml Solution for Injection or Infusion is manufactured by Hamol Ltd UK.

The product is a solution for injection/infusion consisting of the commonly used and well known active substance Oxycodone hydrochloride dissolved in water for injections. Apart from water for injections, the other excipients used are Sodium Citrate and Citric Acid (buffering agents) Sodium hydroxide and Hydrochloric Acid (pH adjusters) and Sodium chloride (tonicity adjuster). Primary container is a glass ampoule (Type I, neutral, clear glass 1ml or 2ml).

II. QUALITY ASPECTS

II.1 Introduction

This application for OxyNorm 10mg/ml Solution for Injection or Infusion is submitted in accordance with Directive 2001/83/EC Article 10 (a) (iii) for a line extension of oxycodone hydrochloride tablets held by the applicant. The national authorisation was granted on 15th December 2006. The product is a solution for injection/infusion consisting of the commonly used and well known active substance Oxycodone hydrochloride.

II.2 2.2 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

II.3.1 Composition

The product is a preservative free, clear, colourless, 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 or 2ml ampoules in a cardboard box.
The drug substance is Oxycodone hydrochloride.
Each ml contains 10 mg of Oxycodone hydrochloride.

The excipients are: Sodium Citrate, Citric Acid, Sodium hydroxide, Hydrochloric Acid, Sodium chloride and Water for Injections.

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II.3.2 Pharmaceutical Development

The drug product is a solution for injection or infusion containing 10 mg/ml of oxycodone hydrochloride.

The product development is adequately described in accordance with the relevant European guidelines.

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 10 mg/ml of oxycodone hydrochloride to complement 3/7 the existing range of 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.

II.3.3 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.

II.3.4 Control of Excipients

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.

II.3.5 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.

II.3.6 Packaging Material

The product is presented in glass ampoules, made of neutral glass, type I with a fill volume of 1ml or 2ml 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.

II.3.7 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 for 3 years.
The product as package for sale does not require any special storage precautions prior to use.
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.
Compatibility/incompatibility with a range of medicinal products likely to be co-administrated with oxycodone hydrochloride has also been assessed.

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 10 mg/ml Solution for Injection or Infusion.

III. NON-CLINICAL ASPECTS

III.1 Introduction

Local tolerance studies have been conducted in rats and rabbits to support parenteral use.

IV. CLINICAL ASPECTS

IV.1 Pharmacokinetics

Two new Phase I studies support the 10 mg/ml injection.

OXI1202 was an open, single dose, four-part, crossover study in 24 healthy male volunteers; it was conducted at a single centre in Northern Ireland from October to November 2000.
Twenty-one subjects completed all four study periods.
The treatment arms were:
Oxycodone injection 10 mg/ml 5 mg intravenous bolus
Oxycodone injection 10 mg/ml 5 mg subcutaneous bolus
Oxycodone injection 10 mg/ml 5 mg intramuscular bolus
Oxycodone IR liquid 5 mg/5 ml (single oral dose)

Table 1 Absorption pharmacokinetics of oxycodone following different routes of administration.
Data are mean and standard deviation factor except for tmax which is median.
Intravenous Subcutaneous Intramuscular Oral liquid

AUCt (ng.h/mL) 109.3 (1.18) 108.5 (1.15) 107.3 (1.17) 49.9 (1.50)
Cmax (ng/mL) 35.3 (1.5) 25.3 (1.2) 22.9 (1.3) 10.4 (1.6)
tmax (h) 0.08 0.5 0.5 1

Study OXI1203 was an open, randomised, four-way, crossover study in 24 healthy, male volunteers it was conducted at a single centre in Leicester, UK, in January and February 2001.
Twenty-one of the 24 subjects completed all four study periods. There was a washout period of at least six days between treatments.

The treatment arms were:
Oxycodone injection 10 mg/ml intravenous bolus dose 5 mg
Oxycodone injection 10 mg/ml subcutaneous bolus dose 5 mg
Oxycodone injection 10 mg/ml eight hour intravenous infusion 10 mg
Oxycodone injection 10 mg/ml eight hour subcutaneous infusion 10 mg

Table 2 Absorption pharmacokinetics of oxycodone following different routes of administration.
Data are mean and standard deviation factor except for tmax which is median.

Intravenous bolus
Subcutaneous bolus
Intravenous infusion
Subcutaneous Infusion
AUCt (ng.h/mL) 101.7 (1.2) 96.1 (1.2) 192.1 (1.2) 179.3 (1.2)
Cmax (ng/mL) 47.9 (1.8) 26.7 (1.3) 19.3 (1.2) 19.0 (1.2)
tmax (h) 0.03 0.25 8.0 8.2
5/7

IV.2 Pharmacodynamics

Oxycodone is a full opioid receptor agonist which exhibits a weak affinity for ì ä and ê opioid receptors; the oxycodone metabolite, oxymorphone, and morphine show greater affinity.
Clinical studies have demonstrated low oxymorphone plasma concentrations following oxycodone dosing, as well as a significantly stronger relationship between oxycodone concentrations and drug effects than between oxymorphone concentrations and drug effects.
Noroxycodone, the major metabolite of oxycodone, is less than one hundredth the potency of the parent compound, while concentrations of the pharmacologically active oxymorphone are typically 2-3% of oxycodone.

IV.3 Clinical efficacy

Two clinical studies support the application.

Study OXI3201 was a double-blind, parallel group, multicentre study to compare the safety, efficacy and tolerability of intravenous (i.v.) oxycodone with intravenous morphine.

Eligible patients were 18 to 80 years old with acute postoperative pain. The study was carried out at four centres in the UK from June 2001 to April 2002.

Patients were given i.v. bolus doses of 2 mg during stabilisation and thereafter bolus doses of 1 mg on demand with a lock-out period of 5 minutes.

Morphine sulphate was administered in the same manner as the oxycodone.

The primary aim was to show that pain relief at 24 hours post surgery was equivalent between the two treatments. The primary efficacy variable was BS-11 pain scores recorded at rest and on movement or deep breathing 24 hours after the discontinuation of PCA. The Per Protocol population was the primary one.

Pain was assessed using Box Scale-11 (BS-11). BS-11 is a visual analogue scale with 11 boxes representing a scale of 0 = no pain to 10 = worst imaginable pain.

Use of the PCA machine (dose delivered and the number of successful and failed PCA demands), sleep disturbance, quality of sleep, and satisfaction with pain management were evaluated.

Table 3 Primary efficacy variable BS-11 scores 24 hours after PCA discontinuation
Oxycodone (n = 46) Morphine n = 54) Treatment difference
(95% CI)
Per Protocol Population
Movement 4.6 (2.6) 4.1 (2.0) 0.55 (-0.37, 1.48)
At rest 2.1 (1.8) 1.5 (1.3) 0.65 (0.02, 1.27)
ITT Population
Movement 4.5 (2.5) 4.3 (2.2) 0.24 (- 0.61, 1.09)
At rest 2.0 (1.8) 1.8 (1.7) 0.18 (-0.44, 0.80)

Study OXI4201 was a randomised, double-blind, placebo controlled, parallel-group comparison of the efficacy, safety and tolerability of intravenous oxycodone injection and OxyContin Tablets with i.v. morphine injection and placebo tablets. It was conducted at three UK centres between August 2002 and April 2004.

Eligible patients were females aged 18- 80 years who were scheduled for gynecological laparotomy.

Patients must have been graded as either 1 or 2 under the American Society of Anesthiologists classification system.

The investigational treatment arm was oxycodone hydrochloride.
Patients received an initial i.v. bolus which was titrated until the patient was judged to be clinically comfortable. Further medication was delivered by patient controlled analgesia.
Patients received intravenous medication for a minimum of 24 hours followed by OxyContin 5 mg b.d. for at least 48 hours and a maximum of five days.

The reference (morphine) arm was similar with the exception that oral medication was placebo.

BS-11 pain scores (0-10 score, ranging from no pain to maximum pain experienced) were used to assess the primary measure of efficacy: postoperative pain on movement or breathing deeply 24 hours after PCA discontinuation.
The nul-hypothesis was equivalence of the oxycodone and morphine/placebo regimens.

Table 4 Primary efficacy outcome BS-11 24 hours after PCA discontinuation
Oxycodone (n = 50) Morphine (n = 55) LSM treatment difference
Score breathing/movement at
PCA discontinuation
4.3 (2.7) 4.0 (2.1) NA

Pain score
breathing/movement at 24
hours post PCA
3.4 (2.4) 3.2 (2.0) 0.32 (-0.45, 1.09)

IV.4 Clinical safety

The OxyNorm Injection 10 mg/ml is currently marketed in Cyprus, Denmark, Finland, France, The Netherlands, Norway, Sweden.

The safety data available for the injection is derived from the pharmacokinetic studies OXI1202 and OXI1203 and the clinical efficacy and safety studies in post-operative pain OXI3201and OXI4201.

Forty-two healthy volunteers were studied and 282 patients of whom 128 were treated with oxycodone.
The discontinuation rates for patients as a result of lack of efficacy during the studies was low and was comparable to the comparators.
The primary reason was due to adverse events.

Table 10 shows the percentage of patients discontinuing from each safety study.
Table 5 Percentage Discontinuations

Study No. Treatment Discontinuations/ completed
%
Discontinuations
OXI3201 Oxycodone 4/64 6
Morphine 5/69 7
OXI3202 Oxycodone 4/15 27
Morphine 2/13 15

IV.5 Discussion on the clinical aspects

Please see V below.

V. OVERALL CONCLUSIONS

OxyNorm 10 mg/ml solution for injection or infusion is a satisfactory formulation of a well known opioid analgesic which is supported by adequate data to demonstrate that it is a safe and effective product.
An Irish national authorisation has already been granted and approval under Mutual Recognition could be granted without need for the generation of further pre-clinical or clinical data.
Follow-up measure: An EU Risk Management Plan for oxycodone hydrochloride parenteral formulations was submitted to fulfil post-authorisation commitments on the 8th January