Decentralised Procedure

Public Assessment Report

Oxycodon-HCl Sandoz 5/10/20 mg Retardtabletten
Kancodal HEXAL 5/10/20 Retardtabletten
Oxycodonhydrochlorid- 1 A Pharma 5/10/20 mg Retardtabletten

Oxycodone hydrochloride

DE/H/1154-1156/001-003/DC

Applicant: Sandoz Pharmaceuticals GmbH
Hexal AG
1 A Pharma GmbH

Reference Member State	DE

TABLE OF CONTENTS

ADMINISTRATIVE INFORMATION

Proposed name of the medicinal product in the RMS	Oxycodon Sandoz 5/10/20 mg Retardtabletten Oxycodon-HEXAL 5/10/20 mg Retardtabletten Oxycodon-1A Pharma 5/10/20 mg Retardtabletten
INN (or common name) of the active substance(s):	Oxycodone hydrochloride
Pharmaco-therapeutic group (ATC Code):	N02AA05
Pharmaceutical form(s) and strength(s):	Prolonged release tablets, 5/10/20 mg
Reference Number for the Decentralised Procedure	DE/H/1154-1156/01-03/DC
Reference Member State:	Germany
Member States concerned:	AT, BE, DK, ES, FI, IE, NL, NO, SE, SI, SK, UK (CMS varying according to dose strengths and/or procedure number)
Applicant (name and address)	Sandoz Pharmaceuticals GmbH, Raiffeisenstr. 11, D-83607 Holzkirchen, Germany Hexal AG, Industriestraße 25, 83607 Holzkirchen, Germany 1A Pharma GmbH, Keltenring 1 +3, 82041 Oberhaching, Germany
Names and addresses of manufacturers of dosage form	Salutas Pharma GmbH Otto-von-Guericke-Allee 1 D-39179 Barleben, Germany
Names and addresses of manufacturers responsible for batch release in the EEA	Salutas Pharma GmbH Otto-von-Guericke-Allee 1 D-39179 Barleben, Germany with manufacturing site Otto-von-Guericke-Allee 1, D-39179 Barleben Salutas Pharma GmbH Otto-von-Guericke-Allee 1 D-39179 Barleben, German with manufacturing site Dieselstrasse 5, 70839 Gerlingen Lek Pharmaceuticals d.d Verovskova 57, 1526 Ljubljana Slovenia

I. INTRODUCTION

Based on the review of the data and the Applicant's response to the questions raised by RMS and CMS on quality, safety and efficacy, the RMS and CMS approved the application for Oxycodone hydrochloride 5 mg/-10 mg/-20 mg prolonged-release tablets in the treatment of severe pain, which can be adequately managed only with opioid analgesics.

II. EXECUTIVE SUMMARY

II.1 Problem statement

This application is submitted in accordance with Article 10(1) of Directive 2001/83/EC. The originator product, OxyContin depottabletit, was first approved in EU member state Finland. The products under discussion are generic to the originator products already marketed in several European countries.

Germany, the Reference Member State within this Decentralised Procedure, also acted as Reference Member State within the Mutual Recognition Procedure DE/H/0366/01-05 dealing with the originator prolonged release tablets containing 5, 10, 20, 40 and 80 mg of oxycodone (Oxygesic®).

II.2 About the product

Classified as belonging to step 3 according to the WHO analgesic ladder, oxycodone is a widely used and well established opioid analgesic. It has been shown to be as effective as morphine in the management of severe to most severe pain, i.e. for the treatment of cancer pain, post-operative pain and non-malignant pain.

Oxycodone acts as an agonist at my, kappa and delta receptors with no antagonist properties. The pharmacological actions of oxycodone are common to all opioid analgesics, which produce their major effects on the central nervous system (brain and spinal cord) and smooth muscles.

The indication of the above mentioned medicinal products applied for under the scope of this Decentralised Procedure is the treatment of severe pain, which can be adequately managed only with opioid analgesics

II.3 General comments on the submitted dossier

The originator´s Oxycodone hydrochloride prolonged release formulations, marketed by Mundipharma throughout the European Union, under the trade names OxyContin® or Oxygesic® are single unit formulations. These formulations are orally administered twice daily, i.e. in 12 hours intervals.

The applicant has developed single unit formulations containing 5-20 mg of the drug substance with similar prolonged release characteristics.

The clinical dossier contains a single- and multiple dose study in fasted state and a single-dose study in fed state for the 10 and 20 mg oxycodone dose strengths.

For the 5 mg strength only a single-dose study under fasted conditions has been performed. The applicant justifies the omission of bioequivalence studies for additional dose strengths under the conditions as laid down in the 'Note for Guidance on the Investigation of Bioavailability and Bioequivalence' (CPMP/EWP/QWP/1401/98) for immediate-release formulations, which also apply for modified-release formulations.

II.4 General comments on compliance with GMP, GLP, GCP and agreed ethical principles.

The RMS has been assured that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture and assembly 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.

III. SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 Quality aspects

DRUG SUBSTANCE

The active substance oxycodone hydrochloride is described in the European Pharmacopoeia (Ph. Eur.). The quality of the drug substance oxycodone hydrochloride is controlled in compliance with the corresponding monograph of the European Pharmacopoeia (Ph Eur).

DRUG PRODUCT

The objective was the development of a product, stable and essentially similar to the innovator product.

The prolonged-release of the drug substance is caused by the following excipients:glycerol(mono, tri)docosanoat, medium-chain triglycerides and hydrogenated castor oil..

Oxycocodone hydrochloride is intended for treatment of severe pain.

The questions raised during the evaluation belong to the pharmaceutical development, manufacturing process as well as to the stability of the drug product.

The ingredients and the manufacturing process of the drug product are considered suitable to produce a pharmaceutical product of the proposed quality.

All relevant quality characteristics of the drug substance and the drug product (release and shelf-life) are specified. The proposed limits are accepted.

The description of the analytical methods used to analyse the drug substance and drug product are adequate, the validation results are plausible.

III.2 Nonclinical aspects

Oxycodone hydrochloride is a substance with well-known pharmacodynamic, pharmacokinetic and toxicological properties. No new information has been provided which would from a non-clinical point of view change the positive risk/benefit assessment of the active substance.

Pharmacodynamics

Oxycodone is an opioid agonist with primarily affinity to μ opiate receptors. It is indicated for the treatment of severe pain.

Pharmacokinetics

Oxycodone is well absorbed from the gastrointestinal tract. Metabolism takes place mainly in the liver via CYP3A4 and CYP2D6 isoforms. Main metabolites are noroxycodone, oxymorphone and several glucuronide conjugates. Excretion is via urine and faeces.

Oxycodone crosses the placenta and is excreted into breast milk. The milk: plasma ratio was calculated to be 3.4:1.

Toxicology

The most severe acute toxic effect of oxycodone is respiratory depression. If Oxycodone is used repeatedly tolerance as well as physical and psychological dependence may develop.

There is insufficient data on reproduction. No data on fertility and postnatal effects following

intrauterine exposure is publicly available. Oxycodone did not cause malformations in rats and rabbits at dosages of 8 mg/kg body weight/day and up to 5 mg/kg body weight/day respectively (corresponding to 1.5 to 2.5 times of the human dose of 160 mg/day, based on mg/kg basis). Experience with the use of oxycodone during human pregnancy is insufficient and does not allow a final assessment.
Most opioid analgesics enter the foetal brain. Thus the administration of oxycodone during pregnancy may cause respiratory depression and/or withdrawal symptoms in the new-born.
Oxycodone shows clastogenic potential *in vitro* assays. However, similar effects were not observed under in vivo conditions even at toxic doses. Altogether, it can be concluded that oxycodone has no clinical relevant genotoxic potential.
Long-term carcinogenicity studies have not been performed.

SPC
The proposed SPC adequately reflects the actual scientific knowledge on oxycodone hydrochloride for the relevant indications and is considered acceptable. There are no objections to approval of *Oxycodone 5, 10 and 20 mg prolonged release tablets* from a non-clinical point of view.

III.3 Clinical aspects

Pharmacokinetics
The pharmacokinetic characteristics of the originator products are: the dose range is linear for the 10 – 80 mg strengths, the formulations are bioequivalent.. Bioequivalence with the originator product has been investigated conducting a total of six in-vivo studies:

- A single-dose bioequivalence trial of the 5 mg test and reference product in fasted healthy volunteers (Study Code: 2006-49-RTA-1)
- A single-dose bioequivalence trial of three 10 mg oxycodone PR tablet formulations (two different test biobatches plus reference) under fasted and fed conditions in healthy volunteers (Study Code: 2005-27-RTA-1)
- A single-dose bioequivalence trial of the 10 mg test and reference product in healthy volunteers under fed conditions (Study Code: 2006-14-RTA-3)
- A single and multiple-dose trial of the 10 mg test and reference product in fasted healthy volunteers (Study Code: 2005-62-RTA-2)
- A single and multiple-dose bioequivalence trial of three 20 mg oxycodone PR tablet formulations (test, Oxygesic® and OxyContin® as references) in healthy volunteers under fasting conditions (Study Code: 2006-50-RTA-1)
- A single-dose bioequivalence trial of three 20 mg oxycodone PR tablet formulations (test, Oxygesic® , OxyContin®) in healthy volunteers under fed conditions (Study Code: 2006-69-RTA-3)

As European reference products in these bioequivalence studies Oxygesic 5 mg, 10 mg, 20 mg, prolonged release tablets, Mundipharma,, were used and in case of the 20 mg studies an additional arm with OxyContin 20 mg prolonged-release tablets, Mundipharma Pty Limited Australia was added.
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The study design, analytical methodology and statistical evaluation of the bioequivalence studies for the prolonged release tablets were appropriately designed and conducted in compliance with the recommendations of the relevant guidelines for GCP and GLP.

Plasma concentrations of oxycodone were determined by validated and specific analytical methods using HPLC with MS/MS detection. The lower limit of quantification (LLOQ) was determined as 0.5 ng/ml. Linearity could be shown over the concentration range from 0.5 ng/ml to 100.0 ng/ml for oxycodone.

For the 10 mg and 20 mg strengths the entire bioequivalence data set (single dose fasted, single dose fed and multiple dose) has been provided. Results of comparative in-vitro dissolution have been provided that demonstrate similarity of the in-vitro dissolution profiles of the 5 mg and 10 mg strengths, thus justifying extrapolation of in-vivo bioequivalence data in the case of the 5 mg strength. The results of the six bioequivalence studies demonstrate interchangeability of the test and reference formulation for all three dose strengths in clinical practice.

Pharmacodynamics
Not applicable

Clinical efficacy
Not applicable

Clinical safety
The adverse events observed during the bioequivalence studies were typical for the administration of strong analgesics to opioid naïve healthy volunteers. Mainly, they comprised nausea, vomiting, and dizziness and occurred with about the same frequency in the test and the reference group. The adverse event profile of oxycodone in the six bioequivalence studies is adequately addressed under section 4.8 of the submitted SPC.

Pharmacovigilance system

All aspects of the Guideline on Monitoring of Compliance with Pharmacovigilance Regulatory Obligations and Pharmacovigilance Inspections (version March 06 public consultation) and of Volume 9A are adequately addressed.

Germany is aware that Volume 9A does not ask for examinations evaluating the success of training systems, it is however a requirement of the German AMWHV (a regulation on GMP) and the global drug safety department of Sandoz is located in Germany. We appreciate that the implementation of an e-learning tool comprising a proficiency test is planned for 2008.

IV. BENEFIT RISK ASSESSMENT

The benefit/risk ratio is positive and therefore the RMS has considered that the application for Oxycodone hydrochloride 5 mg/-10 mg/-20 mg prolonged-release tablets in the treatment of severe pain, which can be adequately managed only with opioid analgesics is approvable.