IPAR

Public Assessment Report for a
Medicinal Product for Human Use

Scientific Discussion

Oxydon 10 mg Prolonged-release tablets
OXYCODONE HYDROCHLORIDE
PA0711/115/005

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.

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I. INTRODUCTION

This product was initially authorised under procedure number DE/H/1419/002 with the DE as RMS. The responsibility of RMS was transferred to Ireland on 23/12/2020 under procedure number IE/H/1157/002/DC.
Please note the following detail for the product in IE:
Marketing Authorisation Number: PA0711/115/005
Marketing Authorisation Holder: Sandoz

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

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

INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the application for Oxycodone Hydrochloride 5 and 10 mg prolonged release tablets in the treatment of severe pain, which can be adequately managed only with opioid analgesics, in adults and adolescents 12 years of age and older is approved.

I. EXECUTIVE SUMMARY

I.1 Problem statement

This decentralised application concerns a generic version of oral prolonged release formulations of oxycodone hydrochloride under the trade names Oxycodone Hydrochloride 5 mg / 10 mg Prolonged-Release Tablets. In this Assessment Report, the name Oxycodone Hydrochloride 5 mg / 10 mg Prolonged-Release Tablets is used.

The data for this application are presented in accordance with Article 10.1 of Directive 2001/83/EC (formerly: Article 10.1 (a) (iii) as amended). The originator product, OxyContin 40 mg depottabletit, was first approved in EU member state Finland on 1996/01/08.

Germany, the Reference Member State within this Decentralised Procedure, also acted as Reference Member State within several other finalised Decentralised Procedures.

I.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 μ-, κ- and δ-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.

I.3 General comments on the submitted dossier

The 5 and 10 mg strengths are identical regarding qualitative aspects of the tablet composition and are dose-proportional with regard to the active substance. One clinical trial program has been undertaken for the 5-10 mg strengths.

Considering the pharmacokinetic characteristics of the originator products (linearity in the dose range of 10 – 80 mg, bioequivalence of the formulations) one clinical trial program for 5/10 mg including four bioequivalence studies with the reference product OxyContin 5/10 mg prolonged release tablets (Napp Pharmaceuticals Ltd., UK) has been investigated.

Main parts of the overall concept of the clinical trial program has been discussed during two scientific advice meeting at national authorities (The Netherlands, Germany) and is considered to meet the requirements of the Note for Guidance on Modified Release Oral and Transdermal Dosage Forms: Section II (Pharmacokinetic and Clinical Evaluation), CPMP/EWP/280/96 and Note for Guidance on the Investigation of Bioavailability and Bioequivalence, CPMP/EWP/QWP/1401/98.

As a result of recently finalised graduated plan procedures with comparable oxycodone-containing medicinal products, concerns have arisen regarding the question to what degree the prolonged release properties of opioid formulations are compromised if the tablets are taken together with alcoholic

beverages in terms of dose dumping and consecutive increased risk of adverse events like e.g. respiratory depression or somnolence.

I.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.

II. QUALITY ASPECTS

II.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). The suitability of the monograph to test the drug substance has been sufficiently verified

DRUG PRODUCT

The Oxycodone Hydrochloride 5/10mg CD formulations are manufactured by compression of oxycodone pellets coated with polymeric membrane of mainly ethylcellulose which controls the drug release from the pellets.

Oxycocodone hydrochloride is intended for treatment of severe pain.

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.

The shelf life of 12 months for the 5/10 mg strength with the storage precaution "do not store above 30° C" when stored in Alu/PVC/PVDC-blisters (40g/m^2) for the 5mg strength and in Alu/PVC/PVDC (90g/ m^2) for the 10 mg formulation or when stored in HDPE bottles is accepted.

III. NON-CLINICAL ASPECTS

II.2 Nonclinical aspects

Oxycodone hydrochloride is a substance with well-known pharmacodynamic, pharmacokinetic and toxicological properties. No new information is available which would from a pre-clinical point of view change the positive risk/benefit assessment of the product. The proposed SPC adequately reflects the actual scientific knowledge on oxycodone hydrochloride for the relevant indications and is considered acceptable. There are hence no objections to approval of "Oxycodone Hydrochloride 5 mg/10 mg Prolonged-Release Tablets" from a non-clinical point of view.

IV. CLINICAL ASPECTS

II.3 Clinical aspects

This application concerns two strengths (5 and 10mg prolonged release tablets) of the active substance oxycodone. The four bioequivalence studies were performed with the 10 mg strength (under fasted, fed and steady state conditions each) and for the 5 mg strength under single dose fasted conditions.

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 a suitable, validated and specific analytical methods. The lower limit of quantification (LLOQ) was appropriate for the purpose. Linearity could be shown over an adequate concentration range.

The results of the four bioequivalence studies point to interchangeability of the test and reference formulation in clinical practice. The 90% confidence interval (CI) for C_{max}, AUC_t and AUC_∞ (ratios of the means of the test and reference formulation) were entirely within the bioequivalence acceptance range of 0.80 to 1.25.

The type II variation DE/H/0790/001-003/II/002 for Oxycodone Ratiopharm 20, 40 and 80 mg prolonged release tablets to include the use in patients between 12 and 17 years of age was mutually approved on 24th July 2008. Therefore, the applicant updated the current product information for 5 and 10 mg prolonged release tablets.

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, vertigo, dizziness and itching and occurred with about the same frequency in the test and the reference group. The adverse event profile of oxycodone in the four bioequivalence studies is adequately addressed under section 4.8 of the submitted SPC.

Most recently, concerns have arisen regarding the question to what degree the prolonged release properties of this formulation are compromised if the tablets are taken together with alcoholic beverages in terms of dose dumping. The applicant was requested to generate data on the in-vitro dissolution behaviour of the prolonged release tablets in the presence of increasing concentrations of alcohol.

In-vitro dissolution data generated by the applicant demonstrated that up to 30 min the release of oxycodone in the absence of alcohol and the presence of 40% of alcohol is increased by about 10% (20% release compared to 30% release). The release rate of oxycodone after 30 min without alcohol and in the presence of 20% of alcohol is nearly identical. The release rate of the originator product Oxycontin already amounts to about 35% after 30 min under standard in vitro release conditions. Even in a prevailing 20% alcohol concentration for 60 min, the release rate of oxycodon is increased by about 15% only (from about 25% without alcohol to about 40% in 20% alcohol). When evaluating the magnitude of these figures after 60 min, it is important to bear in mind that the release rate of the innovator product already amounts to more than 45% in the absence of alcohol. The following considerations have additionally been taken into account in weighing the potential risk for the patient in case of inappropriate use:

- alcohol increases secretion of gastric fluids (contributing to further dilution)
- alcohol is rapidly absorbed from the gastrointestinal tract with a great portion of absorption already taking place in the stomach
- given the about 50 ml of gastric fluids found in the stomach in the resting state and considering the aforementioned particularities of alcohol absorption, it is hardly imaginable that 40% alcoholic concentrations are achievable and maintainable for over 30 min in the stomach. Therefore, the in-vitro dissolution conditions are assumed not to be transferable to the in-vivo situation the generic PR tablets are not monolithic but multi-unit formulations that rapidly disintegrate into small pellets of oxycodone. Due to their small size, these pellets are supposed to rapidly leave the stomach and enter the small intestine. The passage into the small intestine is expected to bring about further extensive dilution of the alcohol concentration in view of the larger fluid volumes prevailing in this part of the gut.

Based on the considerations outlined above, it is estimated that additional warning notes are to be included in the SPC and PIL although this warning note exclusively refers to the inappropriate use of the PR tablets. Regarding the SPC (4.2 and 4.4) and the PIL the proposed wording accurately follows the text proposed by the German competent authorities acting as RMS (DE/H/666) in context with a graduate plan procedure ["Stufenplanverfahren"] that has been finalised in the meantime. With regard to the physiological characterisation of prevailing alcohol concentrations in the stomach after consumption of alcoholic beverages, reference is also made to the CMD discussion on this topic from June 2008 (DE/H/789/01-03/DC).

Pharmacovigilance system

The Pharmacovigilance system as described by the applicant fulfils the requirements and provides adequate evidence that the applicant 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.

V. OVERALL CONCLUSIONS

III. BENEFIT RISK ASSESSMENT

The application contains an adequate review of published clinical data. Bioequivalence has been shown for strengths 5 and 10mg. The identical clinical dossier has already been evaluated during the recently finalised DC procedures.

The current product information for 5 and 10 mg prolonged release tablets was updated to include the use in patients between 12 and 17 years of age after approval of type II variation DE/H/0790/001-003/II/002 for Oxycodone Ratiopharm 20, 40 and 80 mg prolonged release tablets.

Based on the review of the data on quality, safety and efficacy, the application for Oxycodone Hydrochloride 5 and 10 mg prolonged release tablets in the treatment of severe pain, which can be adequately managed only with opioid analgesics is approved.

VI. REVISION DATE

14/03/2022

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 DE/H/1419/002 to IE/H/1157/002			