Decentralised Procedure

Public Assessment Report

Oxycodon comp.-AbZ
5 mg/2,5 mg, 10 mg/5 mg, 20 mg/10 mg, 30 mg/15 mg, 40 mg/20 mg Retardtabletten

Oxycodone hydrochloride/ Naloxone hydrochloride dihydrate

DE/H/4259+4264/001-005/DC

Applicant: Teva B.V.

Reference Member State	DE

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ADMINISTRATIVE INFORMATION

Proposed name of the medicinal product in the RMS	Oxycodon comp.-AbZ 5 mg/2,5 mg, 10 mg/5 mg, 20 mg/10 mg, 30 mg/15 mg, 40 mg/20 mg Retardtabletten
Name of the drug substance (INN name):	Oxycodone hydrochloride + Naloxone hydrochloride dihydrate
Pharmaco-therapeutic group (ATC Code):	N02AA55
Pharmaceutical form(s) and strength(s):	Prolonged release tablet
Reference Number(s) for the Decentralised Procedure	DE/H/4259+4264/001-005/DC
Reference Member State:	DE
Concerned Member States:	**DE/H/4259/001,004-005/DC:** BE, ES, FI, HR IS, IT, PL, SE, SK, UK **DE/H/4259/002-003/DC:** BE, BG, ES, FI, HR, IS, IT, PL, SE, SK, UK **DE/H/4264/001-005/DC:** ES
Applicant (name and address)	Teva B.V. Swensweg 5 2031 GA Haarlem Netherlands

I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the application for *Oxycodon comp.-AbZ 5 mg/2,5 mg, 10 mg/5 mg, 20 mg/10 mg, 30 mg/15 mg; 40 mg/20 mg Retardtabletten*, indicated for severe pain which can be adequately managed only with opioid analgesics and for second line treatment of patients with severe to very severe idiopathic restless legs syndrome after failure of dopaminergic therapy, is approved.

II EXECUTIVE SUMMARY

II.1 Problem statement

This decentralised application concerns a generic version of a fixed 2:1 ratio combination of oxycodone HCl and naloxone HCl, under the trade name Oxycodone comp.-AbZ Retardtabletten. In this Assessment Report, the name OXN PRT is used.

The originator product is Targin 2.5/1.25, 5/2.5, 10/5, 15/7.5, 20/10, 30/15 and 40/20 mg Prolonged release tablets by Mundipharma. The first dose strengths of the Targin product line (10/5 mg and 20/10 mg) are registered in Germany since 2006-05-30.

With Germany as the Reference Member State in this Decentralized Procedure, Teva B.V. is applying for the Marketing Authorisations for OXN PRT in BE, BG, ES, FI, HR, IS, IT, PL, SE, SK, and UK.

II.2 About the product

OXN prolonged release tablets is a fixed-combination product containing the opioid analgesic oxycodone hydrochloride and the opioid-receptor antagonist naloxone hydrochloride dihydrate in a prolonged release system.

Classified as a WHO step III opioid analgesic, oxycodone is used for the treatment of moderate to severe cancer and non-cancer pain. The activity of oxycodone is mainly based on binding to the μ- and κ-opioid-receptor which are widely distributed in the body. Whereas pain relief is predominantly attributed to the oxycodone's μ-receptor agonist activity in the CNS, oxycodone also binds to the μ-receptor in the gut wall, which potentially leads to an inhibition of the propulsive gut motility and the secretion resulting in opioid-induced bowel dysfunction (OBD). OBD is an often severe adverse drug reaction (ADR) related to strong opioid analgesic therapy such as oxycodone that limits the continuous treatment of pain patients (Miyoshi and Leckband, 2001).

The second component in this fixed combination, naloxone, acts antagonistically at opioid receptors with a higher binding affinity than most opioids. Orally administered naloxone reversibly binds to the μ-receptors in the gut and competitively inhibits the binding of opiates to these receptors. In this case, the motility and the secretion status of the small intestine and colon are improved. Following oral administration naloxone has a particularly low systemic bioavailability (<3%) due to a high first-pass effect (Heinzow and Lüllmann 1979, Weinstein et al., 1973). Due to its low systemic availability after oral administration, naloxone exerts its antagonistic properties mainly at the μ-receptors in the gut wall.

Targin PR tablets are indicated

- for severe pain, which can be adequately managed only with opioid analgesics and
- for second line treatment of patients with severe to very severe idiopathic restless legs syndrome after failure of dopaminergic therapy.

The opioid antagonist naloxone is added to counteract opioid-induced constipation by blocking the action of oxycodone at opioid receptors locally in the gut.

II.3 General comments on the submitted dossier

The clinical dossier is well structured and complete.

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.

GMP active substance
Regarding the statement on GMP for the active substance a statement/declaration is provided from the manufacturer(s) responsible for manufacture of the finished product and batch release situated in the EU.

All bioequivalence and the dose-proportionality study were performed in accordance with GCP after approval by an independent ethics committee and were performed at the same qualified clinical study site and the same certified bioanalytical facility.

The bioanalytical site was audited by the German / Austrian Authority in 2006 and 2011. The site of clinical investigation was audited by the Austrian (2011), French (2003), and German Authority (2006). All authorities concluded that the studies (and the study site) fully complied with GCP.

III SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 Quality aspects

Drug Substance

The active substances Oxycodone hydrochloride and Naloxone hydrochloride dihydrate are described in the European Pharmacopoeia (Ph. Eur.).

The quality of the drug substances are 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 verified by EDQM respectively.

Certificates of Suitability have been granted for each supplier of both active substances.

Drug Product

Objective of development program was to obtain a prolonged release formulation with a combination Oxycodone and Naloxone. The product should be used for twice-daily administration in the therapy of severe pain with regard to improvement of opioid-induced constipation (OIC) essentially similar, i.e. bioequivalent with the relevant originator product marketed throughout the European Community under the trade name Targin®/ Targinact® from Mundipharma in Europe.

In addition to the strengths marketed for Targin® (5/2.5 mg, 10/5 mg, 20/10 mg and 40/20 mg) the strength 30/15 mg was developed dose proportionally to the 40/20 mg strength.
The ingredients and the manufacturing process of the drug 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 description of the analytical methods used to analyse the drug product are adequate, the validation results are plausible.

A shelf life of 18 months for the products in the applied strengths is accepted. The precaution advice "Do not store above 25 °C" is considered necessary for the tablets packed in blisters whereas the precaution advice "Do not store above 30°C" is considered necessary for the tablets packed in HDPE bottles.

III.2 Non clinical aspects

Pharmacology, Pharmacokinetics, Toxicology

Pharmacodynamic, pharmacokinetic and toxicological properties of oxycodone and of naloxone as well as those of their combination are well known. As oxycodone and naloxone are widely used, well-known active substances, the applicant has not provided additional non-clinical studies and further non-clinical studies are not required. Overview based on literature review is, thus, appropriate.
The submitted non-clinical overview on the non-clinical pharmacology, pharmacokinetics and toxicology of the combination of oxycodone and naloxone is considered adequate.

Environmental Risk Assessment (ERA)

Since the medicinal products are intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

III.3 Clinical aspects

Pharmacokinetics

To support the application, the applicant has submitted five bioequivalence studies and one dose proportionality study across the entire dose range from 5/2.5 mg to 40/20 mg.
In preparation of the present MAA the applicant sought Scientific Advice both at the EMA and on a national scale at the BfArM.

OXN PRT AbZ and the originator product Targin® are single-unit matrix formulations.

The applicant has conducted the following bioequivalence studies in addition to a dose proportionality study, all in healthy volunteers:

- Comparative bioavailability study of oxycodone and naloxone after **single dose** administration (**fasting** conditions) of Oxycodone HCl 5 mg/Naloxone HCl 2.5 mg PR Tablets (Develco) and Targin 5 mg/2.5 mg Retardtabletten (Mundipharma) in healthy subjects (Study Code: 502B13)
- Comparative bioavailability study of oxycodone and naloxone after **single dose** administration (**fasting** conditions) of Oxycodone HCl 40mg/Naloxone HCl 20mg PR Tablets (Develco) and Targin 40 mg/20 mg Retardtabletten (Mundipharma) in healthy subjects (Study Code 347B13)
- Comparative bioavailability study of oxycodone and naloxone after **single dose** administration (**fed** conditions) of Oxycodone HCl 5 mg/Naloxone HCl 2.5 mg PR Tablets (Develco) and Targin 5 mg/2.5 mg Retardtabletten (Mundipharma) in healthy subjects (Study Code: 503B13)
- Comparative bioavailability study of oxycodone and naloxone after **single dose** administration (**fed** conditions) of Oxycodone HCl 40 mg/Naloxone HCl 20 mgPR Tablets (Develco) and Targin 40 mg/20 mg Retardtabletten (Mundipharma) in healthy subjects (Study Code: 348B13)
- Comparative bioavailability study of oxycodone and naloxone after **multiple dose** administration (fasting conditions) of Oxycodone HCl 20 mg/Naloxone HCl 10 mg PR Tablets (Develco) and Targin® 20 mg/10 mg Retardtabletten (Mundipharma) in healthy subjects (Study Code: 520B13)
- **Dose proportionality** study of oxycodone and naloxone after single dose administration (fasting conditions) of Oxycodone HCl 5 mg/Naloxone HCl 2.5 mg PR Tablets, Oxycodone HCl 10 mg/Naloxone HCl 5 mg PR Tablets, Oxycodone HCl 20 mg/Naloxone HCl 10 mg PR Tablets, Oxycodone HCl 30 mg/Naloxone HCl 15 mg PR Tablets and Oxycodone HCl 40 mg/Naloxone HCl 20 mg PR Tablets (Develco) in healthy subjects (Study code: 021B14)

Similar in vitro dissolution profiles were demonstrated across the series of test product tablet strengths.

There are differences in the quantitative composition between the lower and the higher strengths and differences in shape between the lowest (round) and the remaining strengths (oblong). Instead of conducting single dose fasted studies for each strength, a bracketing approach was followed.
Due to the differences in shape of the tablets (5 mg strength “round” shaped, the remaining ones “oblong” shaped) and the difference in quantitative composition two food effect studies on the extremes of the different strengths, i.e. on OXY/NLX 5/2.5 mg vs Targin® 5/2.5 mg and on OXY/NLX 40/20 mg vs Targin® 40/20 mg were conducted.

With regard to multiple dose data, one multiple dose study may be sufficient and predictive for the whole series of strengths if single dose data in fasted state indicate that the different strengths of test formulations exhibit comparable release characteristics. In case of the strong opioid oxycodone, it is acceptable not to conduct the steady state study with the highest strength for safety reasons to prevent the study population of healthy opioid-naïve subjects from unnecessary risks.

In summary, overall adequacy of the PK study programme (single dose fasted/fed of the extremes 5/2.5 and 40/20, steady state study with the 20/10 mg tablet) is given and is supported by the outcome of the single dose proportionality study of all strengths across the entire dose range. Bioequivalence between the test and the reference tablet was demonstrated after single dose administration of the 5/2.5 mg tablet and 40/20 mg tablet under fasting and fed conditions. Also, the multiple dose study demonstrated bioequivalent plasma concentrations under steady state conditions for the 20/10 mg tablet.

The dose proportionality study demonstrated dose proportional increases in plasma concentrations after single dose administration across the entire tablet dose range (5/2.5, 10/5, 20/10, 30/15, 40/20 mg), which supports the general PK study programme following the strength biowaiver approach.

Overall, it is concluded that bioequivalence between the five strengths of the test product and the reference Targin PR Tablets was adequately demonstrated.

Clinical safety
In-vitro dissolution in the presence of increasing ethanol concentrations revealed that no alcohol-induced dose dumping is to be expected in case the PR tablets are taken with alcoholic beverages contrary to the product label.

Legal Status
POM

User Testing
Overall, the test methodology follows the guidelines of the European Commission (*Guideline on the readability of the label and package leaflet of medicinal products for human use,* Revision January 2009; Update of Directive 2001/83/EC as amended by Directive 2004/27/EC / *Guidance concerning consultations with target patient groups for the packet leaflet*, May 2006). Both the first and the second test round met the success criteria of 90% of the subjects being able to locate the requested information, and of those, 90% being able to give the correct answer, to indicate that they understood the information presented. The general impression of the PL (Content, language and layout) was mostly positive. In conclusion, the user test is accepted.

Summary Pharmacovigilance system
The applicant has submitted a signed Summary of the applicant's Pharmacovigilance System. Provided that the Pharmacovigilance System Master File fully complies with the new legal requirements as set out in the Commission Implementing Regulation and as detailed in the GVP module, the RMS considers the Summary acceptable.

Risk Management Plan
The applicant has submitted a RMP, in which the following safety concerns have been identified by the applicant:

Important identified risks	• Respiratory depression • Drug dependence and withdrawal • Abuse, misuse and diversion • Constipation • Diarrhoea

Important potential risks	• Ileus/Bowel obstruction • Atrial fibrillation and other cardiac events • Serotonin syndrome induced by interaction between oxycodone and serotoninergic drugs • Drug Induced Liver injury
Missing information	• Safety of use during pregnancy and lactation • Safety and efficacy of use in paediatric patients < 18 years • Safety and efficacy in patients with hepatic or renal impairment • Safety and efficacy in long-term use

No additional pharmacovigilance or risk minimisation activities have been proposed.

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the RMS;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

The applicant commits to submit a post approval variation to update the applicant's RMP to bring it into line with that of the reference product (Targinact) in terms of additional risk minimisation measures.

Periodic Safety Update Report (PSUR)

With regard to PSUR submission, the MAH should take the following into account:

- PSURs shall be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal. Marketing authorisation holders shall continuously check the European medicines web-portal for the DLP and frequency of submission of the next PSUR.
- For medicinal products authorized under the legal basis of Article 10(1) or Article 10a of Directive 2001/83/EC, no routine PSURs need to be submitted, unless otherwise specified in the EURD list.
- For medicinal products that do not fall within the categories waived of the obligation to submit routine PSURs by the revised pharmacovigilance legislation, the MAH should follow the DLP according to the EURD list.

IV BENEFIT RISK ASSESSMENT

Bioequivalence between the five strengths of the test oxycodone/naloxone PR tablets and the reference Targin PR tablets was shown. The proposed SmPC is acceptable from the clinical perspective. Overall, the benefit-risk-balance for the product being subject of this procedure is regarded as positive. The application is approved.

For intermediate amendments see current product information.