Decentralised Procedure

Public Assessment Report

Targin 2,5mg/1,25 mg, 15mg/7,5mg, 30mg/15mg Retardtabletten
Oxycodone hydrochloride / Naloxone hydrochloride dihydrate

DE/H/1612/005-007/DC

Applicant: Mundipharma GmbH

Reference Member State	DE

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ADMINISTRATIVE INFORMATION

Proposed name of the medicinal product(s) in the RMS	Targin 2,5 mg/1,25 mg ; 15 mg/7,5 mg ; 30 mg/15 mg Retardtabletten
INN (or common name) of the active substance(s):	Oxycodone hydrochloride / Naloxone hydrochloride
Pharmaco-therapeutic group (ATC Code):	N02AA55
Pharmaceutical form(s) and strength(s):	prolonged-release tablet ; 2,5 mg/1,25 mg ; 15 mg/7,5 mg ; 30 mg/15 mg
Reference Number(s) for the Decentralised Procedure	DE/H/1612/005-007/DC
Reference Member State:	DE
Member States concerned:	AT, BE, BG, CY, CZ, DK, EE, ES, FI, FR, HU, IE, IS, IT, LU, LV, NL, NO, PL, PT, RO, SE, SI, SK, UK
Applicant (name and address)	Mundipharma GmbH Mundipharma Str. 2, D-65549 Limburg, Germany

I. INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the application for *Targin 2,5* mg/1,25 mg, 15 mg/7,5 mg und 30 mg/15 mg Retardtabletten in the treatment of severe pain, which can be adequately managed only with opioid analgesics, is approved.

II. EXECUTIVE SUMMARY

II.1 Problem statement

This decentralised procedure concerns an application for an extension of existing MAs for the fixed combination of oxycodone HCl and naloxone HCl, marketed as *Targin 5 mg/2,5 mg, 10 mg/5 mg, 20 mg/10 mg und 40 mg/20 mg Retardtabletten*.

Targin prolonged release tablets (herein referred to as OXN PR) is a fixed-combination product containing the opioid analgesic oxycodone hydrochloride and the opioid-receptor antagonist naloxone hydrochloride dihydrate in a prolonged release system.

The first marketing authorisation for the combination products OXN10/5 mg PR and OXN20/10 mg PR was granted 2006 in Germany on 31 May. After subsequent MR procedure DE/H/1545 the applicant achieved extension of the dose range by adding the lowest (5/2.5 mg) and highest dose strength (40/20 mg) within the scope of preceding DC procedure DE/H/1612/01-04. In support of the highest 40/20 mg dose strength a further pivotal phase III study (OXN3006) was conducted extending the maximum daily dose to 40/20 mg twice daily.

With Germany as the Reference Member State in this Decentralized Procedure, Mundipharma is applying for the Marketing Authorisations for *Targin 2,5 mg/1,25 mg, 15 mg/7,5 mg und 30 mg/15 mg Retardtabletten* in AT, BE, BG, CY, CZ, DK, EE, ES, FI, FR, HU, IE, IS, IT, LU, LV, NL, NO, PL, PT, RO, SE, SI, SK, and UK as Concerned Member States.

II.2 About the product

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). It is primarily associated with constipation but also with abdominal cramping, bloating and gastroesophageal reflux (Pappagallo 2001). Gastrointestinal adverse events (AE), summarized as OBD, may occur during short-term or long-term opioid use and are characterized clinically by (1) hard, dry stools, (2) straining, (3) incomplete evacuation, (4) bloating, (5) abdominal distention, and (6) increased gastric reflux. The mechanisms for these effects are multifactorial, encompassing both the opioid and non-opioid neuro-modulatory systems.

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.

The present DC procedure DE/H/1612/05-07/DC covers a range of three newly developed dose strengths (2.5/1.25 mg, 15/7.5 mg, 30/15 mg) that are intended to complement the existing four different fixed-combination dose strengths: 5/2.5, 10/5, 20/10, and 40/20 mg with the first figure representing the oxycodone- and the second figure representing the naloxone-amount. The two intermediate dose strengths of OXN15/7.5 mg PR and OXN30/15 mg PR as well as a fine-tuning dose strength OXN2.5/1.25 mg PR are intended to allow a more precise dose titration and to ease individual OXN PR therapy with the goal to treat pain patients with the lowest required dose and, consequently, avoiding unnecessary side effects.

In particular, OXN2.5/1.25 mg PR, representing the lowest dose strength, is intended to further improve therapeutic options for physicians and patients by enabling a flexible and individualised pain therapy. Consequently, the intended use of OXN2.5/1.25 mg PR, as it is the case for OXN5/2.5 mg PR, is for dose titration when initiating opioid therapy, the creation of intermediate doses (e.g., OXN12.5/6.25 mg PR twice daily) and tapering off when opioid treatment is no longer required.

II.3 General comments on the submitted dossier

With the exception of study OXN1506 and *in-vitro* dissolution data of all newly submitted dose strengths in comparison with already marketed dose strengths, no further data are presented in this submission. All information provided in previous regulatory procedures is considered fully relevant for the current submission including the three new dose strengths (OXN2.5/1.75 mg PR, OXN15/7.5 mg PR, OXN30/15 mg PR) and not presented in this dossier.

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.
The Applicant confirms that the PK study OXN1506 was performed in full compliance with ICH and all applicable local Good Clinical Practice (GCP) and regulations. All required study documentation will be archived as required by regulatory authorities.

III. SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 Quality aspects

Drug substance

The active substance oxycodone hydrochloride and naloxone hydrochloride dehydrate are described in the European Pharmacopoeia(Ph. Eur.). The quality of the drug substances (oxycodone hydrochloride and naloxone hydrochloride dihydrate) 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. A Certificate of Suitability has been granted for both active substances.

Drug Product

The objective of the development program was to produce a combination product of oxycodone and naloxone, having a comparable prolonged-release profile to Oxycontin®/Oxygesic® tablets (oxycodone prolonged-release tablets). Preclinical and clinical data show that naloxone administered orally antagonises the effects of opioids on bowel function such as prolonged gut transit time. The agonist/antagonist combination may also reduce the Intravenous and Intranasal abuse potential of the product. These data were the basis for the development of a prolonged-release combination tablet of oxycodone hydrochloride and naloxone hydrochloride in a ratio of 2:1. The ingredients and the manufacturing process of the drug product in the strength of 2.5/1.25 mg, 15/7.5 mg, and 30/15 mg 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 36 months with the precaution advice “do not store above 25 °C” is accepted.

III.2 Non-clinical aspects

Pharmacology, Pharmacokinetics and Toxicology

Prolonged-release combination products containing oxycodone and naloxone in a 2:1 ratio have been marketed under the tradename Targin® since October 2006 for pain treatment with the additional benefit of naloxone counteracting opioid-induced constipation. The applicant has submitted full non-clinical testing programs for each of oxycodone and naloxone either alone or in combination with the initial Marketing Authorisation Application. The nonclinical testing program supported the safety of OXN PR in doses up to 40/20 mg twice daily (80/40 mg total) and equally supports the safety of the 3 new dosage strengths at the highest daily dose of 30/15 mg twice daily (60/30 mg total) subject to this submission. Additional non-clinical studies are not required.

Environmental Risk Assessment (ERA)

Since the proposed maximum daily doses of 80 mg oxycodone hydrochloride and 40 mg naloxone hydrochloride still remain the new strengths will not lead to an increase in the environmental exposure. The applicant's conclusion is supported that the results of the already provided environmental risk assessment are also relevant for the new strengths and therefore no further action is required.

III.3 Clinical aspects

Pharmacokinetics

Study OXN1506 was an open-label, single-dose, 7-treatment, 5-period, randomised incomplete crossover study to demonstrate dose proportionality between the approved dose strengths and the three new dose strengths proposed for marketing authorisation. Two additional strengths were included in this clinical study, which are not subject to this submission. Their inclusion strengthened this investigation of dose-proportionality across a wider range of strengths. Study medication was administered under single dose fasted conditions.

The primary objective of the study was to assess the pharmacokinetics and dose proportionality of five new and two existing (10/5 mg and 40/20 mg) strengths of OXN PR tablets.

Secondary analyses also applied MMRM models with fixed terms for treatment, sequence, period and a random term for subject. The relative dose-adjusted systemic bioavailabilities (Frelt, and FreIINF) were calculated from the ratios of AUCt and, where possible AUC_{INF} values. Dose-adjusted Cmax ratios were also calculated.

For oxycodone, each of the OXN PR test treatments provided an equivalent dose-adjusted availability to the reference treatment in terms of AUCt and AUC_{INF}. Geometric mean ratios for the comparisons ranged from 100.3–105.8% for AUCt. Associated 90% CI values were all within the 80–125% acceptance limits. For AUC_{INF}, geometric mean ratios for the comparisons ranged from 100.1–108.4%. Associated 90% CI values were also within the limits of acceptability for BE.
Dose-adjusted Cmax ratios were equivalent for all comparisons, with the exception of the 2.5/1.25 mg treatment, where the geometric mean ratio was 127.6%, and the upper 90% CI fell above the 125% limit for BE at 133.4%. Geometric mean ratios from the other treatments ranged from 101.0–118.7%, with associated 90% CI were within the limits of acceptability for BE.

For naloxone-3-glucuronide, each of the OXN PR test treatments provided an equivalent dose-adjusted availability to the reference treatment in terms of AUCt, AUC_{INF} and Cmax.

The Applicant applies for a line extension and intends to justify transfer to the clinical data package of the existing product range by conducting one combined linearity / bioequivalence study under single dose fasted conditions for the newly developed formulations.

In line with section 5.1 of the Guideline for Modified Release Oral Dosage Forms, CPMP/EWP/280/96, a single dose fasted study is required for each strength in case of PR single unit formulations with multiple strengths. Studies at steady state may be conducted with the highest strength only, if the same criteria for extrapolating bioequivalence studies are fulfilled as described in the Guideline for immediate release forms (see section 4.1.6 of Guideline 1401/98 Rev.1).

With regard to the absolute and relative tablet formulation components, three distinct groups of related strengths are discernible. For each of these groups, the food effect was tested in separate studies. The observed food effect was very similar across the groups with AUC increased by about 15% and Cmax increased by about 27-42% after ingestion of a standardised high-fat meal.

A multiple-dose study was conducted with the highest currently approved 40/20 mg tablet strength. The observed AUCτ for one 12-h dosing interval was in good agreement with the AUC observed in several single dose studies of the 40/20 mg tablet. Furthermore, as evidenced by the across study comparison across a total of 13 PK studies, Cmax and AUC values are predictable and follow linear kinetics. The multiple-dose data generated for the highest 40/20 mg strength are therefore considered representative for the entire range of available tablet strengths.

In terms of dose-proportionality / linearity, both for oxycodone and naloxone-3-glucuronide proportional increases in the extent of absorption (AUC) were demonstrated with increasing doses of OXN PR tablets.

In terms of maximum plasma concentrations, however, dose proportional increases with dose could not be shown after administration of the lowest 2.5/1.25 mg tablet strength. The 90% CIs for the comparison on Cmax between the 2.5/1.25 mg and the 40/20 mg tablet exceeded the BE acceptance range (point estimator 127,6 [122.0, 133.4]) in the newly conducted dose proportionality study OXN1506.

Clinical safety
It was demonstrated by *in-vitro* dissolution data that no dose dumping occurs in the presence of increasing alcohol concentrations.

Assessment of User Testing
A Bridging Report was provided in order to bridge readability testing of the daughter PLs Targin 2,5 mg/1,25 mg, 15 mg/7,5 mg, 30 mg/15 mg Retardtabletten to the package leaflet for the 20/10 mg tablet strength that was user tested in 2007.
From the results of the Readability User Test, it can be concluded that most patients who are prescribed Targin® 20/10 mg prolonged-release tablets will be able to find and understand the sought information in the PL. The PL for Targin® 20/10 mg prolonged-release tablets achieved satisfactory results. The user tested PL for Targin® 20/10 mg prolonged-release tablets is acceptable as readable and comprehensible according to the guidelines of the European Commission.

Pharmacovigilance system
The Applicant/Proposed Future MAH has submitted a signed Summary of the Applicant's/Proposed Future MAH'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

Safety concern	Proposed pharmacovigilance activities (routine and additional)	Proposed risk minimization activities (routine and additional)
Constipation	Routine pharmacovigilance activities	Appropriate labelling in the SmPC and PIL.
Diarrhoea	Routine pharmacovigilance activities	Appropriate labelling in the SmPC and PIL.
Drug withdrawal syndrome	Continue close monitoring for drug withdrawal syndrome and conduct of a cumulative analysis thereof with each OXN PSUR.	The approved SmPCs contain appropriate warnings on drug withdrawal syndrome in section 4.4; these warnings entail specific scenarios (opioid switch, abrupt OXN therapy cessation) as well as a strong warning with regards to the risk of a marked drug withdrawal syndrome in case OXN is abused by individuals dependent on opioid agonists. Also educational materials as focused risk minimization activity may be used in accordance with local customs.
Atrial fibrillation and other cardiac events	Close monitoring for atrial fibrillation. Routine pharmacovigilance monitoring with regards to other cardiac events following use of OXN products.	No risk minimization activities are required.
Abuse, misuse, diversion, drug dependence	Continue close monitoring for abuse, misuse, diversion, and drug dependence and conduct of a cumulative analysis thereof with each OXN PSUR.	The approved SmPCs contains specific paragraphs providing information on the risk of abuse, misuse and drug dependence and also additional warnings with regards to a history of alcohol / drug abuse or addiction disorders as well as any abuse by drug addicts. Also educational materials as focused risk minimization activity may be used in accordance with local
Ileus/bowel obstruction	Close monitoring for ileus/bowel obstruction	No risk minimization activities are required.
Serious hepatic events	Close monitoring for serious hepatic events until 12APR2013	No risk minimization activities are required.

Periodic Safety Update Report (PSUR)
Oxycodon + Naloxone is found in the EURD list. The PSUR submission frequency is 13 years. The next DLP is 31.05.2025.

IV. BENEFIT RISK ASSESSMENT

From the clinical perspective, it was adequately demonstrated how the newly developed dose strengths (2.5 mg/1.25 mg, 15 mg/7.5 mg, 30 mg/15 mg) pharmacokinetically fit into the range of available tablet strengths. Dose proportionality in terms of AUC was shown over the tablet dose range according to current guideline provisions. Furthermore, post-hoc analyses across a total of 13 separate PK studies demonstrated linear and predictable increases of plasma levels with increasing doses. The benefit risk balance is positive from the clinical point of view.
The application is approved.
For intermediate amendments see current product information.