Decentralised Procedure

Public Assessment Report

Targin 5 mg/2.5 mg, 10 mg/5 mg, 20 mg/10 mg, 40 mg/20 mg
Prolonged release tablets

Oxycodone hydrochloride
Naloxone hydrochloride dihydrate

DE/H/1612/01-04/DC

Applicant: Mundipharma GmbH, Germany

Reference Member State	DE

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ADMINISTRATIVE INFORMATION

Proposed name of the medicinal product in the RMS	Targin 5 mg/2.5 mg, 10 mg/5 mg, 20 mg/10 mg, 40 mg/20 mg prolonged release tablets
INN (or common name) of the active substance(s):	Oxycodone hydrochloride Naloxone hydrochloride dihydrate
Pharmaco-therapeutic group (ATC Code):	Oxycodone hydrochloride: N02 AA05 Naloxone hydrochloride: V03 AB15
Pharmaceutical form(s) and strength(s):	Prolonged release tablets 5 mg oxycodone HCl/ 2.5 mg naloxone HCl 10 mg oxycodone HCl / 5 mg naloxone HCl 20 mg oxycodone HCl / 10 mg naloxone HCl 40 mg oxycodone HCl / 20 mg naloxone HCl
Reference Number for the Decentralised Procedure	DE/H/1612/01-04/DC
Reference Member State:	Germany
Member States concerned:	AT, BE, CY, CZ, DK, ES, FI, FR, IE, IS, IT, LU, NL, NO, PL, PT, RO, SE, UK (not all countries involved for the 10/5 and 20/10 mg strength)
Applicant (name and address)	Mundipharma GmbH, Germany
Names and addresses of manufacturers responsible for batch release in the EEA	Mundipharma GmbH , Limburg Bard Pharmaceutical, Cambridge

I. INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the application for Targin 5mg/2.5mg, 10mg/5mg, 20mg/10mg, 40mg/20 mg prolonged release tablets (herein also referred to as OXN PR or Targin®), in the treatment of severe pain, which can be adequately managed only with opioids, with the naloxone component in the fixed combination with oxycodone being added to counteract opioid-induced constipation by blocking the action of oxycodone at opioid receptors locally in the gut,

is approved.

II. EXECUTIVE SUMMARY

II.1 Problem statement

The first marketing authorisation for the combination products OXN 10/5 mg PR and OXN 20/10 mg PR was granted on a conditional basis according to §28(3) in connection with §21 of the German Drug Law on 31 May 2006 in Germany. OXN PR has been marketed in Germany by Mundipharma GmbH under the brand name Targin® since 02 October 2006.

The provisions of §28 (3) of the German National Drug Law constitute the legal framework for granting approval to a medicinal product while requesting additional clinical data (as commitment) if there is public interest in accelerated market access due to anticipated therapeutic advantage (so-called conditional approval). Since the conditional approval was granted, the requested additional clinical studies have been completely submitted by now. The completed clinical dossier of OXN PR forms the basis for the current DC procedure. At the same time the applicant is applying for extension of the dose range by adding the lowest (5/2.5 mg) and highest dose strength (40/20 mg). In support of the highest 40/20 mg dose strength a further pivotal phase III study (XX01) was conducted.

The first set of formulations tested and emerging from Phase II were prolonged-release tablets with oxycodone and naloxone in the combination 10/5 mg, 20/10 mg and 40/20 mg, respectively. The original marketing authorisation application included all three fixed combinations. OXN 10/5 mg PR and OXN 20/10 mg PR received approval under the auspices of § 28 (3) of the German Drug Law. OXN 40/20 mg PR was not considered approvable without the results of study XX01, which investigates the high-dose fixed combination OXN 40/20 mg PR and that was not completed by that time.

With Germany as the Reference Member State in this Decentralised Procedure (DCP), the Marketing Authorisation Holder, Mundipharma GmbH Germany, is applying for marketing authorisations for Targin 5/2.5, 10/5, 20/10, 40/20 mg prolonged release tablets in AT, BE, CY, CZ, DK, ES, FI, FR, IE, IS, IT, LU, NL, NO, PL, PT, RO, SE, and UK.

II.2 About the product

Targin prolonged release tablets (herein also referred to as OXN PR) is a fixed-combination product containing oxycodone hydrochloride and naloxone hydrochloride 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). 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 neuromodulatory 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.

OXN PR is currently approved for the treatment of severe pain which can be adequately managed only with opioids. The naloxone component in the fixed combination with oxycodone is added to counteract opioid-induced constipation by blocking the action of oxycodone at opioid receptors locally in the gut. The maximum daily dose is 80/40 a day, corresponding to 80 mg oxycodone hydrochloride and 40 mg naloxone hydrochloride, i.e. the twice daily administration of OXN PR 40/20 mg prolonged release tablets. Patients requiring higher doses should be administered supplemental prolonged release oxycodone at the same time intervals, taking into account the maximum daily dose of 400 mg PR oxycodone.

II.3 General comments on the submitted dossier

The overviews as well as the summaries comprehensively present and discuss all relevant issues with regard to the new combination of the known substances oxycodone and naloxone. The overall quality of the expert reports is good. The dossier is complete and contains all relevant data to evaluate the benefit-risk balance of OXN PR.

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.
The applicant assures that all clinical studies were conducted according to current Good Clinical Practice (GCP) standards. Two early pharmacokinetic studies were conducted in the United States, all other clinical studies were conducted in Europe.
As for nonclinical, all pivotal toxicology studies with either the combinations or the single entities were conducted according to Good Laboratory Practice (GLP) regulations.

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 by 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 5/2.5 mg, 10/5 mg, 20/10 mg, 40/20 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 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 24 months for OXN PR 5 mg/2.5mg with the storage precaution “Do not store above 25°C” is acceptable. For the products OXN PR 10/5, 20/10, 40/20 mg prolonged release tablets the claimed shelf life of 36 months with the storage precaution “Do not store above 25°C” is acceptable.

III.2 Nonclinical aspects

The product under discussion is a comparatively new fixed combination of the well known substances naloxone and oxycodone (Oxycodone:naloxone). Pharmacodynamic, pharmacokinetic and toxicological properties of both single entities are well known and widely clinically used.
Oxycodone is available in immediate and prolonged release formulations and is approved in most European countries for the treatment of moderate to severe malignant and non-malignant pain in doses up to 400 mg/day.
Naloxone (Narcanti®) is available as an i.v. solution and is indicated for the complete or partial reversal of opioid effects. It is also used for the diagnosis of suspected acute opioid overdosage. In the combination with the weak opioid receptor agonist Tilidine it is also available as an oral solution and tablets for the treatment of pain (e.g. Valoron® N, Tilidin comp.STADA). Maximum daily dose of Naloxone with no limitation of duration of use administered via these products is comparable to doses administered via Targin.

For the fixed combination of oxycodone:naloxone, there is more limited clinical experience as the dose strengths 10/5 mg and 20/10 mg for prolonged release twice daily application were approved in Germany since 31st May 2006 (authorisation numbers: 64537.00.00 and 64538.00.00) and in various European countries via mutual recognition (DE/H/1545/001-002) since October 2008. The maximum daily doses administered via OXN PR are 80 mg oxyodone and 40 mg naloxone.

The applicant has submitted several non-clinical bridging studies in support of this product.
The bridging programme consists of a primary pharmacodynamic study evaluating the parenteral abuse deterrent properties in a rat model, two i*n vitro* studies investigating drug-drug interaction in human hepatocytes and the inhibition of drug metabolizing enzymes. Furthermore single dose, 7- and 28-day range finding studies and 4-week (GLP compliant) and 3-month (GLP compliant) toxicity studies in rats and dogs were submitted.

In view of the well known single entities the extent of the non-clinical bridging programme as well as design of the studies needed to support development of a fixed combination seems adequate and in line with the relevant GUIDELINE ON THE NON-CLINICAL DEVELOPMENT OF FIXED COMBINATIONS OF MEDICINAL PRODUCTS **(**EMEA/CHMP/SWP/258498/2005). Further testing e.g. investigating genotoxicity, carcinogenicity and reproductive toxicity with the combination of oxycodone:naloxone is not regarded nessecary. This is justified as the single compounds have adequately been tested regarding these endpoints and the combination studies did not show relevant undesirable potential additive, potentiation or antagonistic effects with respect to pharmacology, pharmacokinetics and toxicology.

There is adequate clinical and non-clinical information of pharmacology, pharmacokinetics and toxicology for oxycodone and naloxone as single entities. Therefore, only new data or data of relevance to the combination are discussed here.

Pharmacology

Oxycodone is an opioid analgesic; in contrast, Naloxone is an opioid receptor antagonist. The analgesic effect of oxycodone is largely attributed to binding with the μ- opioid receptors in the CNS. Oxycodone has also an effect on μ-receptors in the GI tract resulting in opioid bowel dysfunction. Naloxone is believed to act as an opioid-receptor antagonist, both in the CNS (central) and the GI-tract (peripheral). Naloxone, like oxycodone and morphine binds with high affinity to μ-receptors and in some studies naloxone has been shown to have a greater affinity than oxycodone for all opioid receptors.

The oxycodone:naloxone combination as a parenteral abuse-deterrent product has been investigated in physically dependent rats. Intravenous oxycodone co-administered with naloxone in a 2:1 ratio precipitated the signs of opioid withdrawal in rats physically dependent on oxycodone and consequently confirmed the parenteral abuse deterrent properties. In separate control groups, the intravenous administration of naloxone alone to oxycodone-dependent animals, resulted in a robust withdrawal that was lasting for several hours.

There were no nonclinical studies investigating the oxycodone:naloxone combinations effects in improving the gastrointestinal effects. These studies were conducted directly in humans.

There is also literature available describing these effects of parenteral administration of opioid:naloxone combinations in opioid-dependent populations.

Pharmacokinetics

Oxycodone has high oral bioavailability; in contrast, Naloxone has very low oral bioavailability due to high first pass deactivation in the liver. In humans, oxycodone and naloxone differ significantly in oral bioavailability (mean values of 87% have been reported for oxycodone vs. < 3 % for naloxone).

Drug interaction of oxycodone:naloxone combination has been investigated in two *in vitro* studies.
The metabolism of oxycodone:naloxone was assessed in human liver microsomes, cytosolic fractions, hepatocytes, and recombinant human CYP-isoforms. Oxycodone and naloxone are metabolised by two

different pathways. Oxycodone metabolism is mostly by CYP3A4 and CYP2D6 isozymes while naloxone is mostly glucuronidated. The results of this study show that at therapeutic concentrations, the oxycodone:naloxone 2:1 ratio formulation would not be expected to cause potential clinical drug-drug interactions with other co-administered drugs metabolised by the following CYP isoforms (CYP1A2, CYP2A6, CYP2C9/19, CYP2D6, CYP2E1 and CYP3A4).
A second *in vitro* study was conducted using human hepatocytes to evaluate the potential metabolic interactions between oxycodone and naloxone, and between the combination of other drugs that are likely to be co-administered with the combination product. The selection of the drugs for this study acetylsalysilic acid and acetaminophen was based on their metabolic pathway and on the fact they were often included in pain management. Naltrexone was selected to support the clinical program for OXN PR. The results showed that neither naltrexone, acetaminophen nor acetyl-salysilic acid were found to inhibit oxycodone metabolism.

For the oxycodone:naloxone combinations, *in vivo* pharmacokinetics were assessed as part of the pharmacodynamics study in rats and the toxicology and toxicokinetic studies in rats and dogs.
Data indicate that the plasma exposure to the two components increased proportionally to the increase in dose. Pharmacokinetics and metabolism for each of oxycodone and naloxone following oral administration were not affected by the presence of the other component at doses ranging from 4:0.34 to 200:100 mg/kg in rats and from 0.3:0.026 to 10:5 mg/kg in dogs.
The major circulating metabolites were similar in humans, rats and dogs.
The main difference with humans, lies in the oxycodone:naloxone plasma ratios achieved following oral administration. In the rat the mean ratio was the lowest (~30:1) compared to the dog (130:1) while in humans this ratio is 562:1 based on AUC. By contrast, when oxycodone:naloxone at 2:1 ratio was administered intravenously to oxycodone dependent rats, the oxycodone:naloxone plasma ratio in abstinent (exhibiting withdrawal) rats was 4.5:1 based on AUC. These pharmacokinetic differences were adequately considered in the toxicological studies.

Toxicology

Toxicology bridging studies were conducted with oxycodone:naloxone combinations at 2:1 and 12:1 ratios. The combination with the 12:1 ratio was evaluated because there were significant differences in the plasma exposure ratio of oxycodone:naloxone for the toxicology species (rat and dog) compared with humans when all species received the 2:1 combination.
Toxicology studies consisted of single and multiple dose oral range-finding studies in rats and dogs; one-month definitive oral studies with oxycodone:naloxone at 2:1 ratio in rats and dogs; and three-month definitive oral studies in rats and dogs with oxycodone:naloxone at a 12:1 ratio. Toxicokinetic parameters were evaluated in all single dose and definitive repeat dose studies. The one-month definitive oral studies with oxycodone:naloxone at 2:1 ratio in rats and dogs and the three-month definitive oral studies in rats and dogs with oxycodone:naloxone at a 12:1 ratio were performed in accordance with GLP principles.

Available toxicological data do not indicate that there will be potential additive toxicity / toxicity unique to the combination, previously not seen for the single compounds administered alone.

It should also be mentioned that recently during a generic DCP a Potential Serious Risk to Public Health regarding the genotoxic potential of oxycodone was raised by one CMS. Therefore, the genotoxic potential of oxycodone has been discussed here in more detail.
For oxycodone, both the mouse lymphoma assay and the lymphocyte study showed positive results with oxycodone. Whereas in the chromosomal aberration test and the mouse lymphoma assay without S9 mix effects occurred at very high clinically not relevant concentrations only, in the mouse lymphoma assay with S9 mix an increased frequency of mutant colonies were observed already at 50 µg oxycodone/ml. Thus, both *in vitro* mammalian assays indicate a chromosome damaging potential for oxycodone. Although the mechanism for the *in vitro* observed chromosomal damaging effects at high doses are not ultimately understood, the negative results from an *in vivo* study using high exposure levels relative to therapeutic exposure suggest that these effects are *in vitro* specific and very unlikely to occur under conditions of clinical use at doses administered via OXN PR.

In addition, the *in vitro* genotoxicity profile of oxycodone resembles that of many other well known and widely used opioids which were found to be in vitro clastogens without showing corresponding positive effects *in vivo* studies. These *in vitro* findings were evaluated as not indicative of a genotoxic hazard. A similar assessment of the genotoxicity data of oxycodone appears to be justified. In our opinion available data do not suggest that oxycodone may present a more unfavourable profile than related substances with comparable indication (e.g. morphine showed positive results in an *in vivo* study). Furthermore, a recent publication evaluating genotoxicity-related structural alerts confirms the currently accepted assessment that oxycodone and related compounds does not represent a relevant genotoxic risk to patients.
In accordance to current ICH guidelines, a further *in vivo* test may be recommended as there were positive *in vitro* results. However, as no new data are available, which would change the current assessment that oxycodone has no clinical relevant genotoxic activity, the *in vivo* study used has been properly conducted in the most appropriate test to investigate the effects observed *in vitro* and as reference can be made to mutagenicity data of related opioides which support the assessment of the positive *in vitro* findings, such further testing seems not considered necessary.
Overall, available data indicate that oxycodone has no relevant genotoxic activity under the conditions of clinical use. The current assessment has not changed and at present further *in vivo* testing seems not considered necessary.

To fill gaps in the non-clinical reproduction testing the applicant has recently completed the non-clinical reproduction testing battery and has submitted a Fertility and Early Embryonic Development to Implantation in Rats (GLP-compliant) and an oral Pre- and Post-Natal Development Study in Rats (GLP-compliant). Both additional studies have already been disscussed in several DCPs (e.g. DE/H/366/13/II and DE/H/366/14) and MRP of oxynal (DE/H/1545/001-002).
Reproductive toxicology studies can be summarised as follows:
In rats oxycodone had no effect on fertility/reproduction, on the early embryonic development of the rat, or adverse effects on gestation, parturition and lactation of the F0 females or on the development of the F1 pups and their survival, physical development, behavior and reproductive performance.
Oxycodone was not teratogenic in rats or rabbits in doses of up to 8 mg/kg (rat) and 5 mg/kg (rabbit), however in rabbits, when individual fetuses were used in statistical evaluation, a dose related increase in developmental variations was observed (increased incidences of 27 presacral vertebrae, extra pairs of ribs). When these parameters were statistically evaluated using litters, only the incidence of 27 presacral vertebrae was increased and only in the 125 mg/kg group, a dose level that produced severe pharmacotoxic effects in the pregnant animals.
Oyxcodone showed no clinically relevant effect on fertility and early embryonic development. Mentionable findings in this study were that the number of implantation sites and live embryos in the 8 mg/kg/day group were statistically lower compared to the control group. However, these values remained within the historical control ranges and were therefore considered not to be of clinical relevance.
The oral prenatal and postnatal development study had been conducted in rats with daily doses of 0.5, 2.0, and 6.0 mg oxycocdone hydrochloride per kilogram body weight from gestation day 6 until weaning. Pharmacologic activity of oxycodone hydrochloride in form of exaggerated pharmacologic reactions like increased or decreased activity, excessive licking/grooming, chewing on paws, limbs, tail, and cage bedding could be observed at all dose-levels tested in the F0-generation. Body weights and food consumption were affected at doses ≥ 2 mg/kg/d. F1 body weights at 6 mg/kg/d were lower when compared to body weights of the control group. There was neither effect on physical, reflexological, and sensory developmental parameters nor on behavioural and reproductive indices.

SPC has been adequately updated with this data and is essentially in line with the texts of the recently completed MRP of Oxynal (DE/H/1545/001-002) which was agreed following extensive discussion with several CMSs and RMS.

The submitted environmental risk assessment does not meet the requirements of the guideline on the environmental risk assessment of medicinal products for human use (EMEA/CHMP/SWP/4447/00, June 2006). At the present time it is not possible to complete the environmental risk assessment for the active ingredients oxycodone hydrochloride and naloxone hydrochloride. The applicant has acknowledged the need for additional data regarding the environmental risk assessment. Therefore the

applicant indicates that a series of studies will be conducted according to the guideline on the environmental risk assessment of medicinal products for human use for both oxycodone and naloxone. The presentation of the Phase II risk assessment has been focussed on May 2010.

In summary, taken into account data from the literature, clinical data, post marketing surveillance (see clinical overview), and non-clinical studies with the single entities and the combination of oxycodone:naloxone, it can be concluded that OXN PR is safe if used under the conditions mentioned in the SPC.
Sections 4.6 and 5.3 of SPC are essentially in line with the recently completed MRP of oxynal (DE/H/1545/001-002). The applicant has given a commitment that the outstanding studies on environmental toxicity and Phase II risk assessment will be submitted until May 2010.

In conclusion, **OXN 5/2.5, 10/5mg, 20/10mg and 40/20mg prolonged release tablets** is approved from a non-clinical point of view.

III.3 Clinical aspects

Pharmacokinetics

After oral administration, naloxone is rapidly inactivated through hepatic first-pass glucuronisation. Thereafter, the parent substance naloxone is barely detectable in the plasma. For the purpose of the PK studies, the metabolite naloxone-3-glucuronide is used as a surrogate parameter.

These results of study XX02 confirm the interchangeability of the fixed combination tablets across the range of doses administered (4 x OXN 10/5, 2 x OXN 20/10, 1 x OXN 40/20). Each of the 90% confidence intervals for the ratio of population geometric means (test vs reference) for AUCINF, AUCt and Cmax of oxycodone and naloxone-3-glucuronide fell within the 80% - 125% acceptance range. The fixed combination tablets were also shown to be bioequivalent to Oxygesic given together with naloxone CR tablet (2 x Oxygesic 20 plus 2 x naloxone PR 10).

In the multiple dose study XX03, steady state conditions were confirmed by examining the trough concentrations for oxycodone and naloxone-3-glucuronide, and showing them to be no longer rising on Day 4, the pharmacokinetic sampling day. The aim of the study was to show bioequivalence between OXN 40/20 and oxycodone from oxycodone PR tablet 40 mg, and naloxone-3-glucuronide from naloxone CR tablets 2 x 10 mg at steady state. This was achieved for oxycodone; the bioavailability comparisons between the combination product and the single entities met the criteria for bioequivalence, showing that administering oxycodone and naloxone as a combination product at steady state had no effect on the pharmacokinetics of oxycodone.

Study XX04 was conducted to examine the absolute bioavailability of naloxone in case of abusive intranasal application of OXN after crushing the tablets (absolute availability of naloxone after p.o administration approx. 3%).After intranasal administration the absolute availability of naloxone amounts to about 27-32%. In view of this considerably high systemic availability of the opioid antagonist naloxone after abusive i.n. application of OXN and the consecutive occurrence of opioid withdrawal symptoms in opioid addicted subjects, explicit warning notes were implemented in the current SPC to highlight naloxone's potential to induce withdrawal symptoms after any kind of OXN abuse.

Similar in-vitro dissolution profiles for all OXN dose strengths have been shown. Almost ideal dose linearity for oxycodone (when administered from a mono-entity product) is well established. Within the fixed-combination, naloxone does not appear to interfere with the absorption profile of oxycodone as proven by study XX05 which demonstrated bioequivalence between OXN 5/2.5 mg and Oxy PR 5 mg. Inter-study-comparison of various single dose studies demonstrated linearity for oxycodone when administered from OXN in the range of 5/2.5 to 40/20 mg. Overall, the PK profile of the newly

submitted 5/2.5 mg strength that is complementary to the PK characterisation of the other three strengths was adequately characterised.

Furthermore, PK studies in special populations (elderly, renal and hepatic impairment) were conducted. The PK results are adequately reflected under section 5.2 of the SPC. Respective warning notes resp. contraindications (moderate to severe hepatic impairment) have been implemented. Following ingestion of a high-fat breakfast, the bioavailability and peak plasma concentration of oxycodone were increased by an average of 16% and 30% respectively compared to administration in the fasting state. The issue is adequately reflected under section 5.2 of the proposed SPC.

Clinical efficacy

In the dose finding phase II study XX06 different combination ratios (from 1:1 to 8:1) of oxycodone and naloxone and placebo groups were tested up to maximum doses of 80 mg oxycodone and 40 mg naloxone. The primary efficacy parameters were patient assessment of pain intensity (mean pain) and patient's assessment of bowel function (based on ease of defecation, feeling of incomplete bowel evacuation and judgement of constipation).

The dose-ratio of 2:1 oxycodone/naloxone in patients needing opioid-therapy is justified by the data of the dose-finding study XX06 and the appropriateness has been further confirmed in the pivotal Phase III studies

The efficacy of OXN PR was investigated in three Phase III studies (XX07, XX08 and XX01). Study XX07 compared placebo and OxyPR with the combination product OXN PR, while XX08 and XX01 compared OxyPR to OXN PR.

Study XX07 provides evidence that OXN PR is superior to placebo with regards to pain relief. The times to pain event were significantly shorter in the placebo group compared to the OXN PR group. No statistically significant differences could be seen between the OXN PR and OxyPR group.

Study XX08 (dose range 20-50 mg oxycodone) and study XX01 (dose range 60-80 mg oxycodone) provide evidence that OXN PR is superior to OxyPR with regards to bowel function, and particularly with regards reducing constipation. The difference is statistically significant and clinically relevant. The evidence seen in the primary BFI analysis is further confirmed by the statistically significant treatment differences in the number of CSBMs, as well as the PACOI, including constipation symptoms and bothersomeness (PAC-SYM and PAC-SYM(b), which also favour treatment with OXN PR. The increase in number of CSBMs is particularly relevant for patients requiring chronic pain treatment. The demonstrated improvement in bowel function is achieved without sacrificing any of the analgesic efficacy of the oxycodone component.

Overall, the efficacy data provided in this dossier confirm the superior pain relief of OXN PR compared to placebo, the comparable pain relief of OXN PR compared to OxyPR, and the improved bowel function of OXN PR compared to OxyPR.

Clinical safety

OXN PR is generally well tolerated. The overall adverse event profile of OXN observed during the phase II and phase III trials, the 12-month open label extension studies and the first PSUR reports after marketing is typical for opioid analgesics. Due to the combination with naloxone, particular focus was set upon diarrhoea (particularly occurring after treatment initiation) and possible induction of opioid

withdrawal symptoms. The incidence of both AE was low and does not give rise to particular safety concerns. Section 4.8 of the SPC adequately reflects the AE profile both observed with the new fixed combination and the profile already known for oxycodone if administered alone.

Adverse events reported in the clinical study programme and during the first Post Marketing experience primarily affected the gastrointestinal system. Constipation, nausea, headache, vomiting and diarrhoea were the most frequently reported AEs. The number of subjects with gastrointestinal AEs was comparable across all treatment groups. The number of subjects experiencing diarrhoea was generally low, transient in duration and comparable across all treatment groups in the three pivotal studies.

It was proven by in-vitro dissolution testing that increasing alcohol concentrations up to 40% for up to 120 min do not adversely affect the prolonged release properties of the tablets. However, with regard to the general pharmacological interaction between oxycodone and alcohol, that is applicable to all oxycodone-containing medicinal products, additional warning notes to the labelling and package leaflet were implemented according to a recent press release of the CMDh from November 2008.

Pharmacovigilance system

Description of Pharmacovigilance System

Based on the Detailed Description of the Pharmacovigilance System which was submitted to the authorities during the procedure the RMS considers that the applicant has a Pharmacovigilance system in place which is in accordance with the requirements as described in Volume 9a of Rules Governing Medicinal Products in the European Union.

Risk Management Plan

A brief overview of non-clinical, clinical and post marketing studies is provided. No safety concerns that have not been adequately addressed by clinical data or which are of unknown significance were identified.

The Risk Management Plan provided by the applicant was generally accepted. The identified and potential risks suggested by the applicant are endorsed. The RMP largely meets the formal requirements of the *Guideline on Risk Management Systems for Medicinal Products for Human Use* and *Annex C: Template for EU Risk Management Plan.* For future versions of the RMP however, the applicant committed to make use of the tables as specified in *Annex C: Template for EU Risk Management Plan.*

In consideration of the abuse potential of oxycodone the applicant committed to closely monitor all reports of abuse, misuse, diversion, dependence, and withdrawal and to present a cumulative analysis, including severity and outcome of the reaction, with every PSUR.

In addition, the applicant committed to provide to physicians and healthcare professionals educational information outlining the risks of abuse, misuse, dependence, withdrawal on cessation of treatment and acute withdrawal in the case of parenteral application according to local requirements and custom, if required prior to launch of the respective products.

IV. BENEFIT RISK ASSESSMENT

OXN 5/2.5 mg PR, OXN 10/5 mg PR, OXN 20/10 mg PR and OXN 40/20 mg PR tablets have been investigated in a battery of Phase I studies. OXN 10/5 mg PR, OXN 20/10 mg PR and OXN 40/20 mg PR tablets were also subject to three Phase III studies including approximately 1100 patients. OXN PR tablets have proven efficacy in the claimed indication.

The analgesic efficacy of OXN 10/5 mg PR, OXN 20/10 mg PR and OXN 40/20 mg PR is statistically significantly superior to placebo and non-inferior to pain therapy with oxycodone monotherapy.

Statistically significant improvement of bowel function with regards to preventing and/or reducing opioid-induced constipation was shown for OXN PR in comparison to oxycodone monotherapy.
A broad safety data pool for OXN PR is available including information from clinical studies, the prospective observational cohort study as well as its post approval use in pain patients in Germany.
The benefit risk ratio of OXN PR in the dose range up to 80/40 mg per day appears positive. The application for MA of OXN 5/2.5, 10/5, 20/10 and 40/20 mg prolonged release tablets is therefore approved.