Australian Government

Department of Health and Ageing

Therapeutic Goods Administration

Australian Public Assessment Report for Oxycodone hydrochloride/Naloxone hydrochloride

Proprietary Product Name: Targin

Submission No: PM-2008-2938-1

Sponsor: Mundipharma Pty Ltd

May 2010

Contents

I. Introduction to Product Submission

Submission Details

Type of Submission	New Fixed Combination
Decision:	Approved
Date of Decision:	5 March 2010
Active ingredient(s):	Oxycodone hydrochloride, naloxone hydrochloride (as the dihydrate)
Product Name(s):	Targin
Sponsor's Name and Address:	Mundipharma Pty Ltd GPO Box 5214 Sydney NSW 2001
Dose form(s):	Modified release tablets
Strength(s):	5/2.5, 10/5, 20/10 & 40/20 mg
Container(s):	PVC/Al blister packs
Pack size(s):	20 (all strengths)
Approved Therapeutic use:	Management of moderate to severe chronic pain unresponsive to non-narcotic analgesia. The naloxone component in a fixed combination with oxycodone is indicated for the therapy and/or prophylaxis of opioid-induced constipation.
Route(s) of administration:	Oral
Dosage:	Daily doses of up to 40/20 mg Targin, twice daily, are usually sufficient but higher doses may be required

Product Background

OXN PR is a fixed-combination product, formulated as a tablet, containing oxycodone and naloxone in a prolonged release system. Oxycodone is an opioid analgesic that is used for the treatment of pain. After oral intake, naloxone is expected to prevent the development, or to reduce the duration and severity, of opioid-induced bowel dysfunction (OBD), mainly opioid induced constipation (OIC), without interfering with the analgesic efficacy of oxycodone.

The activity of oxycodone is mainly based on binding to the μ- and additionally to κ-receptors. Pain relief is predominantly attributed to the μ-receptors in the central nervous system (CNS). Oxycodone also binds to the μ-receptors in the gut wall, which leads to an inhibition of the propulsive gut motility and to a modification of secretion and fluid absorption resulting in OBD. OBD is an often severe adverse drug reaction (ADR) related to strong opioid analgesic therapy such as oxycodone. OBD is primarily associated with constipation but also with abdominal cramping, bloating and gastroesophageal reflux. Constipation is the most frequently reported ADR.

Naloxone is an opioid receptor antagonist. It is commercially available as a single entity in intravenous (IV) dosage forms, which are indicated for the blockade of exogenously administered opioids. An oral dosage form of the single entity naloxone is not available in any market. Naloxone acts antagonistically and binds to opioid receptors with a higher affinity than most opioids. This also occurs with the μ-receptors in the gut wall.

Combining oxycodone and naloxone in a fixed combination has the potential advantage of providing sufficient analgesic efficacy while reducing and/or preventing opioid-induced constipation. This may provide an overall superior pain therapy compared to opioid monotherapies.

In Australia, oxycodone hydrochloride (HCl) is currently registered by Mundipharma in a number of dosage forms, is available in immediate and prolonged release formulations and is marketed as OxyContin tablets and Oxynorm capsules, oral solution and injection. Oxygesic (the trade name for prolonged-release oxycodone in Germany) has been approved in Germany since 1998 for the treatment of pain.

Naloxone HCl is registered as an injection by a number of companies for the treatment of opioid overdose. It is also present in Suboxone (buprenorphine HCl and naloxone HCl) sublingual tablets as a deterrent to abuse of the product by injection (naloxone produces marked opiate antagonist effects and opiate withdrawal when injected, but its bioavailability by the oral and sublingual routes is extremely low).

The proposed product is a new fixed dose combination of oxycodone HCl and naloxone HCl and is formulated as a modified release tablet. The naloxone is primarily present for the treatment and/or prophylaxis of opioid-induced constipation, but it would also be expected to deter abuse of the product by injection.

The therapeutic indication proposed by the sponsor for Targin is as follows:

The management of moderate to severe chronic pain unresponsive to non-narcotic analgesia. The naloxone component in a fixed combination with oxycodone is indicated for the therapy and/or prophylaxis of opioid-induced constipation.

Regulatory Status

Targin prolonged release tablets 10mg/5mg and 20mg/10mg were first approved in Germany in May 2006.. In October 2008 a Mutual Recognition Procedure in the European Union (EU) with Germany acting as the Reference Member State was completed in 13 countries for the same two strengths. A Decentralised Country Procedure in the EU was completed in May 2009 in 20 countries, which included all four strengths. A similar dossier was submitted in Australia.

The combination has been approved in Sweden, UK, the Netherlands, Denmark, Norway, France, Austria, Belgium, Finland, Germany, Iceland, Ireland, Luxembourg, Poland, Portugal, Romania, the Czech Republic with applications pending in Cyprus, Italy and Spain.

It has also been approved in Canada, Switzerland, New Zealand, Israel and Korea.

Product Information

The approved product information current at the time this AusPAR was prepared is at Attachment 1.

II. Quality Findings

Drug Substances (active ingredients)

Both active ingredients are the subject of European Pharmacopoeia monographs and appropriate Certificates of Suitability have been submitted.

Oxycodone HCl is freely soluble in water. At 37°C, its solubility is greater than 20% at pH 5 and greater than 1% at pH 7.5. Its octanol/water partition coefficient (log P) is 0.7, and its pKa is 8.9.

Naloxone HCl is soluble in water (> 3.3%). Its octanol/water partition coefficient (log P) is 1.5, and its pKa is 7.9.

Neither active ingredient exhibits polymorphism.

The Australian Approved Name (AAN) 'oxycodone HCl' is defined as anhydrous, while the AAN, 'naloxone HCl' is defined as the dihydrate.

Drug Product

Four strengths of modified release tablet are proposed. The four strengths have been developed to give similar *in vitro* release profiles. The release rates of oxycodone and naloxone from Targin tablets are very similar under all circumstances. In vitro studies have demonstrated that the rate of release of the drugs from the tablets is not affected by alcohol. The product contains no unusual excipients.

The tablets are manufactured by a hot melt extrusion process.

The routine quality control dissolution method employs a paddle apparatus. Although level A *in vitro-in vivo* correlation (IVIVC) has been established, the correlation was not used to set the dissolution specification. Instead, it is claimed that the dissolution specification was based on that applied to OxyContin tablets. Questions raised concerning the dissolution specification for Targin tablets were satisfactorily answered by the company.

The release rates of oxycodone and naloxone from Targin tablets are very similar under all circumstances.

A shelf life of 3 years below 25°C is approved for the three higher strength tablets. A shelf life of 2 years below 25°C is approved for the 5/2.5 mg tablets.

Biopharmaceutics

Nine bioavailability studies were submitted. Two were not evaluated.

Study 1403 assessed single dose bioequivalence amongst the three higher strength tablets and against single agent oxycodone modified release tablets (Oxygesic tablets) and single agent naloxone modified release tablets given concomitantly. The primary parameter of concern is the bioavailability of the oxycodone component of Targin tablets. The study showed that the three higher strength tablets are bioequivalent with respect to oxycodone. They also have equivalent area under the plasma concentration time curve (AUC), but an 11-14% lower mean maximal plasma concentration (C_{max}) compared to Oxygesic tablets. In view of the very low oral bioavailability of naloxone, the most appropriate parameter for comparing different treatments with regard to this component is the level of its primary metabolite, naloxone-3-glucuronide. All four treatments were bioequivalent with regard to both AUC and C_{max} with regard to this parameter.

Study 1011 was a steady state study that compared the 40/20 tablet with the above single agent tablets given separately. Oxycodone bioequivalence was demonstrated with regard to AUC, C_{max} and minimal plasma concentration (C_{min}). Naloxone-3-glucuronide bioequivalence was demonstrated with regard to AUC but the mean C_{max} and C_{min} values for the Targin tablet were 11% and 16% lower, respectively, than the single agent tablet.

Study 1008 was a single dose comparison of the 40/20 tablet with oral solutions of oxycodone and naloxone given together. This demonstrated bioequivalence with regard to AUC for both oxycodone and naloxone-3-glucuronide. The C_{max} values for the Targin tablet were only 29-37% of those for the oral solution, as expected for a prolonged release tablet.

Study 1008 also demonstrated that a high fat meal increased the mean oxycodone AUC by 15% and increased the mean C_{max} by 28%. There was no effect on naloxone-3-glucuronide AUC, and a 12% decrease in C_{max}. Similar results were obtained in an analogous study using the 10/5 tablet (Study 1009). No significant dose dumping was evident in the fed state in individual subjects apart from two subjects in Study 1009 who had oxycodone C_{max} values that were 78% and 97% higher in the

fed state compared to the fasted state. However, the overall range of C_{max} values was similar in the fed and fasted states.

Study 1018 was a single dose study that compared the 5/2.5 tablet with single agent oxycodone modified release tablets (Oxygesic tablets) and with oral solutions of oxycodone and naloxone given together. This study also assessed the effect of food on the 5/2.5 tablet. Results were similar to those obtained in other studies, but food increased the mean C_{max} by 42%, which is greater than the increase observed in Studies 1008 and 1009.

Study 1016 (single dose, fasting) demonstrated that batches of 10/5 and 40/20 tablets manufactured at laboratory scale were bioequivalent to corresponding production scale batches. The study also showed that administration of oral naltrexone had no effect on the oxycodone or naloxone-3-glucuronide pharmacokinetic parameters (naltrexone was administered in many of the bioavailability studies, particularly with higher strength oxycodone, in order to block the opiate effects of the oxycodone).

Study 1013 was an IVIVC study (based on oxycodone only, because of the low plasma levels of naloxone). A quadratic *in vitro-in vivo* correlation was established between the *in vitro* dissolution rate and the *in vivo* input rate determined by deconvolution of plasma level curves. Although the mean AUC results increased with increasing dissolution rate, the three tablets were bioequivalent with regard to this parameter. The three tablets were not bioequivalent with regard to C_{max}, which increased significantly with increasing dissolution rate.

Quality Summary and Conclusions

There were no objections on chemistry, manufacturing and controls grounds to registration of Targin tablets.

III. Nonclinical Findings

Introduction

The data presented were of a generally high quality. The critical studies examining repeat-dose toxicity, genotoxicity and teratogenicity were Good Laboratory Practice (GLP)-compliant.

Pharmacology

Primary pharmacodynamics

Rationale

Constipation, abdominal cramp, and nausea are distressing side effects of the use of opioid analgesics for the relief of chronic pain, and can be dose-limiting for the ongoing use of such drugs (McNicol et al. 2003). These problems derive from various opioid-induced intestinal effects including inhibition of peristalsis and intestinal fluid secretion, and increased water absorption from intestinal contents (De Luca & Coupar 1996). Non-specific ameliorative measures, such as use of laxatives, only partly resolve these problems. Opioids act by stimulating opioid receptors, which modulate the wide variety of physiological functions that are influenced by opioids. Activation of opioid receptors on the neurons of the myenteric plexus of the gastrointestinal (GI) tract is responsible for the inhibition of gut motility, whereas activation of receptors in the central nervous system (CNS) mediates the analgesic actions of opioids. Accordingly, selective blockage of gut opioid receptors is a potential means of avoiding opioid-induced bowel dysfunction whilst retaining opioid analgesic action.

In vitro studies

In vitro testing, using cells expressing recombinant human opioid receptors, showed that oxycodone has high selectivity for μ- versus κ-opioid receptors and is a potent stimulator of μ-opioid receptor-dependent functional activities. Some oxycodone metabolites also showed potent receptor

stimulation, but were considered to be present at *in vivo* concentrations too low to be of pharmacological significance. Naloxone was shown to bind strongly to both μ- and κ-opioid receptors but to have little or no ability to stimulate functional activity. The major naloxone metabolite (naloxone-3-glucuronide) showed around 400x lower affinity for the μ-opioid receptor than its parent.

In vivo studies

Studies in the literature have demonstrated the ability of opioid receptor agonist/antagonist combinations to reduce opioid-induced bowel dysfunction in animal models. The sponsor did not attempt to reproduce such studies in animals. The sponsor did demonstrate that intravenous (IV) injection of oxycodone:naloxone (2:1) into oxycodone-dependent rats produced withdrawal-associated behaviours, indicating that Targin tablets would not be attractive to IV drug users.

Secondary pharmacodynamics

Secondary pharmacodynamics of the oxycodone:naloxone combination were not examined. Possible effects of oxycodone, naloxone and their metabolites on cardiac potassium current were examined. Both oxycodone and naloxone produced only modest current inhibition at concentrations ≥ 7x that expected under clinical conditions. Some metabolites of oxycodone/naloxone were more potent current inhibitors, but such effects were seen at concentrations far exceeding expected *in vivo* levels.

Safety pharmacology

Such studies were not performed due to the extensive clinical experience in the use of oxycodone and naloxone.

Pharmacokinetics

Single- and repeat-dose studies

Multiple studies were performed using rats and dogs. Many of the studies were part of a larger toxicology study. Aside from a study of IV infused naloxone, all studies involved oral administration of oxycodone, naloxone or an oxycodone:naloxone combination. Major conclusions from these studies were:

(1) In both rats and dogs, oxycodone and naloxone were rapidly taken up from the gut and metabolised. Times to maximal plasma concentration (T_{max}) were generally around 0.5 hours after dosing.

(2) Noroxycodone was clearly the major metabolite of oxycodone in both rats and dogs, with much lower levels of oxymorphone and noroxymorphone being produced.

(3) Naloxone-3-glucuronide was the major metabolite of naloxone in rats and dogs, with other metabolites present at much lower levels.

(4) Noroxymorphone can derive from both oxycodone and naloxone metabolism, although comparison between dogs dosed with oxycodone:naloxone (2:1) and with naloxone alone suggested that only around 1-2% of noroxymorphone, in combination-dosed animals, derives from naloxone.

(5) AUC and C_{max} values for oxycodone, naloxone, and their metabolites generally increased in direct proportion to dose, over the range tested, in both rats and dogs.

(6) Higher AUC and C_{max} values (typically 2-3 times greater) for oxycodone and naloxone were generally found in female compared with male rats. The latter showed higher values for drug metabolites. There were, however, no sex-related differences in the metabolism of oxycodone and naloxone in dogs.

(7) C_{max} and AUC values for naloxone were comparable between animals dosed with oxycodone:naloxone and with naloxone alone for both rats and dogs. This suggests that oxycodone does not interfere with the metabolism of naloxone.

(8) A 12:1 oxycodone:naloxone ratio gave a pharmacokinetic profile (that is, blood plasma drug exposure levels) in rats and dogs that was comparable to that produced in humans by a 2:1 ratio).

(9) After repeated dosing for weeks or months, there was little evidence for accumulation of oxycodone or naloxone in dogs. Repeat-dosed rats showed some evidence for accumulation (C_{max} and AUC values for oxycodone and naloxone increased up to about 2-fold), although the oxycodone:naloxone ratio did not change markedly during the dosing period.

(10) IV-infused naloxone had a half-life in dogs of around 17-56 minutes that showed no effect of dose, sex, or day of dosing (to a maximum of 15 days).

Protein binding

The binding of oxycodone and naloxone to blood plasma proteins was not studied by the sponsor. There appear to be no studies in the literature on protein binding in animals of oxycodone or naloxone. The sponsor states (without reference) that "in humans, oxycodone is 45% protein bound predominantly to albumin". There is a literature study suggesting that naloxone in humans binds to α_1-acid glycoprotein and perhaps β-lipoprotein.

Tissue distribution

The sponsor did not perform tissue distribution studies. A literature study demonstrated that at 60 minutes after intragastric dosing of rats with oxycodone, there was a 2:1 ratio of drug in brain to blood plasma. For oxycodone metabolites, the ratio was significantly less than one. A literature study of rats given naloxone by subcutaneous (SC) injection demonstrated elimination half-life ($t_{1/2}$) values for brain and blood plasma of 0.4 hours. Other tissues to show significant drug levels included kidney, spleen, lung, heart and skeletal muscle.

Metabolism and excretion

Oxycodone metabolism occurs primarily in the liver and can involve at least five separate pathways. The three most important of these metabolic pathways are: (1) 6-keto reduction to 6α/β-oxycodol; (2) *O*-demethylation to oxymorphone primarily catalysed by cytochrome P4502D6 (CYP2D6); and (3) *N*-demethylation to noroxycodone primarily catalysed by CYP3A4. Oxymorphone can then undergo glucuronidation, whilst noroxycodone can undergo glucuronidation or conversion (via CYP2D6) to noroxymorphone. Noroxycodone was the major circulating metabolite derived from oxycodone dosing in both rats and dogs. Similarly, noroxycodone was the major oxycodone-derived metabolite produced by liver microsomal preparations from a variety of species (including humans).

Naloxone was metabolised in liver through at least three separate pathways: (1) 6-keto reduction to 6α/β-naloxol catalysed by 3α-hydroxysteroid dehydrogenase; (2) glucuronidation to naloxone-3-glucuronide catalysed by UDP-glucuronosyltransferase; and (3) *N*-deallylation to noroxymorphone primarily catalysed by CYP3A4. The conjugation product naloxone-3-glucuronide was the major circulating metabolite of naloxone in both rats and dogs.

Oxycodone and naloxone (alone or in combination) did not inhibit major drug-metabolising cytochrome P450 enzymes from human liver microsomal preparations, suggesting that there is little likelihood for their interference with the CYP metabolism of other drugs. Noroxymorphone (a metabolite of both oxycodone and naloxone) was shown to have no significant inhibitory effect on the CYP enzymes predominantly responsible for oxycodone metabolism (CYP2D6 and CYP3A4).

Excretion studies were not performed by the sponsor. Results from the scientific literature suggest that the various metabolic products of oxycodone and naloxone (see above) are excreted in urine and faeces, with most of the drug eliminated within 2-3 days of dosing.

Pharmacokinetic drug interactions

The possible effect of oxycodone and its metabolites on the metabolism of naloxone, and *vice versa*, was examined in human liver microsomal preparations. Neither drug influenced the metabolism of the other, suggesting that there are unlikely to be interactions between oxycodone and naloxone under *in vivo* conditions.

The effect of drugs that might be used in combination with oxycodone:naloxone on the metabolism of the latter was investigated using *in vitro* cultured normal human hepatocytes. The results suggested that therapeutic levels of naltrexone, paracetamol and acetylsalicylic acid would have little effect on the metabolism of oxycodone and naloxone.

Amitriptyline, an antidepressant that is commonly given to cancer patients receiving opioids for pain relief, is metabolised by CYP2C19 and CYP3A (both CYP enzymes are also involved in the metabolism of oxycodone). Amitriptyline was shown in a literature study to have no effect on the pharmacokinetics of a subsequent oral dose of oxycodone in humans.

A literature study has suggested that oxycodone is not a substrate of P-glycoprotein, and hence its uptake into the brain should not be affected by co-administration of P-glycoprotein substrates.

Toxicology

Relative exposure

An exposure ratio was derived by dividing the animal AUC values by an AUC value from normal humans given the maximum recommended oxycodone/naloxone dose. The maximum recommended daily dose of Targin tablets is 80/40 mg (corresponding to 12-hourly administration of a 40/20 mg tablet containing 40 mg of oxycodone HCl and 20 mg of naloxone HCl). Animal AUC values (mostly AUC_{last}, that is, the area under the curve measured to the last quantifiable time point) were usually averages of two or three determinations made during the dosing period. In rat studies, drug exposure generally increased during the dosing period. Separate exposure ratio values are given for male and female rats at each dose, however, male and female dogs generally had comparable AUC values and the exposure ratios shown for dogs are averages for both sexes.

The human AUC value for oxycodone exposure (978 ng*h/mL), used for exposure ratio calculation, derived from a study in which humans were given a single oral 40:20 mg dose of oxycodone:naloxone. The average value from the latter study was multiplied by two to equate with the human maximum dose of 80 mg per day (i.e. 489 x 2 = 978 ng*h/mL). The calculated oxycodone exposure ratios are very consistent between studies using a given species.

The calculation of naloxone exposure ratios is more problematic because of the low blood plasma levels found after dosing. The sponsor suggests that naloxone AUC values are unreliable and recommends the use of AUC values for the metabolite naloxone-3-glucuronide as a surrogate. However, some studies included determinations of naloxone but not naloxone-3-glucuronide AUC values. In addition, the validity of the proposed substitution of naloxone-3-glucuronide for naloxone AUC values seems questionable (for example it takes no account of possible drug and metabolite half-life differences between species). Accordingly, exposure ratios based on both naloxone and naloxone-3-glucuronide AUC values were calculated. AUC values for naloxone and naloxone-3-glucuronide of 870 pg*h/mL and 520 ng*h/mL, respectively, were determined for humans given a single oral 40:20 mg dose of oxycodone:naloxone. The latter values were multiplied by two (to equate with clinical maximum naloxone dose, 40 mg per day) for use in exposure ratio calculations, that is, 1.74 ng*h/mL and 1040 ng*h/mL, respectively.

Single-dose toxicity

Clinical signs in rats given oral oxycodone:naloxone included decreased activity, protruding eye balls, increased muscle tone, and self-biting. In addition, females showed marked fur loss on the torso. There were no treatment-related effects on body weight or food consumption following oral administration of oxycodone:naloxone at doses as high as 200:100 mg/kg or of oxycodone alone at doses as high as 100 mg/kg. The maximum tolerated dose (MTD) for rats was >200/100 mg/kg. Clinical signs in oxycodone:naloxone dosed dogs included salivation and decreased activity. The MTD for dogs was ≥ 40:20 mg/kg.

Naloxone-alone dosing was performed in mice, rats, and rabbits. The MTD for mice was around 600 mg/kg, with animals showing mild to severe tremors at that dose. One of five male rats died after receiving a naloxone dose of 800 mg/kg, suggesting that the median lethal dose (LD_{50}) is slightly in excess of that dose. The LD_{50} for naloxone in rabbits was around 2500 mg/kg, with animals dying after exhibiting convulsions.

Repeat-dose toxicity

Major repeat-dose studies using orally administered oxycodone, naloxone or oxycodone:naloxone combination were conducted in rats and dogs for various times. In most studies, animals were dosed once per day by gavage or capsule. The key studies were performed by established pharmacology laboratories according to GLP procedures, and used both sexes and standard testing times and group numbers.

Studies dosing rats with oxycodone alone for 28 or 90 days indicated No Observable Adverse Effect Levels (NOAELs) of 4 (corresponding to an exposure ratio of ~0.03-0.1) and around 1.6 mg/kg/day (exposure ratio ~0.01-0.05), respectively. At higher doses, various clinical signs were noted including chewing on limbs and decreased weight gain. The incidence and number of clinical signs was usually greater in female than in male rats, consistent with the more rapid metabolism of oxycodone and naloxone by males. Clinical signs resolved quickly and almost completely after the cessation of dosing. No toxicologically meaningful changes were noted during subsequent necropsy. Dog studies of oxycodone-alone dosing revealed similar outcomes to those found with rats. NOAELs for 28 and 91 consecutive days of dosing were 1 or less (exposure ratio of 0.26) and 1 mg/kg/day (exposure ratio 0.16), respectively. The MTD was 8 mg/kg/day of oxycodone (exposure ratio 1.4). Clinical signs included recumbency, decreased activity, and excessive salivation.

Rats dosed with naloxone alone by oral gavage for 91 consecutive days showed few clinical signs, even at relatively high doses, other than decreased activity and a reduction in weight gain. A NOAEL of 50 mg/kg/day was indicated, however, the study did not include pharmacokinetic measurements and so an exposure ratio could not be determined. Another rat study (whose primary aim was to examine carcinogenicity) involved dosing with naloxone for 2 years. It indicated a NOAEL of 20 mg/kg/day which equated to an exposure ratio of around 50. There are, however, uncertainties associated with the latter values: the rats were dosed with naloxone incorporated into their diet (how does the bioavailability of dietary naloxone compare with that from a bolus dose?) and the estimates of naloxone exposure derived from the measurement of blood plasma levels at a single daily time point (how do plasma levels vary in relation to time after feeding activity?). One of four female dogs receiving oral naloxone at 125 mg/kg/day was sacrificed on Day 3 of dosing after experiencing dosing-related convulsions. The latter animal showed acute haemorrhage in several organs. A NOAEL of 75 mg/kg/day (exposure ratio of 189) was indicated for naloxone-alone dosing of dogs for 39 weeks.

Rat studies using daily oral dosing with oxycodone:naloxone at a 2:1 ratio for 28 days and at a 12:1 ratio for 90 days indicated NOAELs of <5:2.5 mg/kg/day (exposure ratios of <0.04-0.1 and <2-3 for oxycodone and naloxone, respectively) and <4:0.34 mg/kg/day (exposure ratios of <0.04-0.15 and <0.2-0.4), respectively. The major clinical signs for oxycodone:naloxone dosing were similar to those seen for oxycodone-alone dosing and included chewing on limbs and decreases in both food consumption and weight gain. These clinical signs resolved quickly after cessation of dosing. No toxicologically significant findings were made during necropsy of dosed animals. Major dog studies also involved dosing with oxycodone:naloxone at a 2:1 ratio for 28 days and at 12:1 for 90 days. NOAELs of 5:2.5 mg/kg/day (exposure ratios of 1 and 4-5) and 0.3:0.026 mg/kg/day (exposure ratios of 0.07 and 0.1) were determined. Clinical signs included decreased activity and excess salivation. There were no toxicologically significant findings in dosed animals.

Genotoxicity

These studies were conducted using the individual components (that is, oxycodone or naloxone) rather than the combination. In the absence of evidence indicating interaction between the drugs, this approach seems reasonable.

Oxycodone was negative in Ames-type bacterial gene mutation assays performed by two independent laboratories. Testing at the thymidine kinase locus of mouse lymphoma cells showed very weak mutagenic activity by oxycodone that was, however, significantly enhanced by addition of rat liver S9 metabolic activation mix to the assay. The mutant colonies seen in the latter assay were relatively small, suggesting that they arose from clastogenic events. Oxycodone's clastogenic potential was confirmed in studies showing that it could induce chromosomal aberrations in *in vitro*-cultured normal human peripheral blood lymphocytes in the presence (but not in the absence) of rat liver S9 metabolic activation mix. This increase in aberration yields only occurred, however, at very high oxycodone concentrations suggesting that the drug has little potential for chromosomal aberration induction *in vivo*. The latter conclusion was apparently confirmed by *in vivo* studies in which oxycodone was orally administered to mice and the induction of micronucleated erythrocyte precursor cells was examined. No significant increase, relative to controls, in the frequency of micronucleated cells was found.

Naloxone was negative in Ames-type bacterial gene mutation assays performed both with and without rat liver S9 metabolic activation mix. Studies from two independent laboratories demonstrated, however, that naloxone could induce mutations at both the thymidine kinase and hypoxanthine-guanine phosphoribosyltransferase loci of mouse lymphoma cells. The mutagenicity of naloxone was enhanced by rat liver S9 metabolic activation mix and, based on the predominant induction of relatively small mutant colonies, appeared to derive from clastogenic activity. Consistent with the latter result, it was shown that naloxone could induce chromosomal aberrations in *in vitro*-cultured normal human peripheral blood lymphocytes in the presence (but not in the absence) of rat liver S9 metabolic activation mix. As with oxycodone, the induction of chromosomal aberrations by naloxone occurred at relatively high drug concentrations. The micronucleus assay revealed no significant increase in the frequency of micronucleated erythrocyte precursors following oral administration of naloxone to mice.

The above tests were performed according to GLP specifications and used suitable drug concentration ranges and positive controls. The use of S9 metabolic activation mix was appropriate given the basic similarities in oxycodone:naloxone metabolism between rodents and man. Although both drugs showed reproducible genotoxicity in different *in vitro* systems (particularly in the presence of S9 metabolic activation mix), their potential for *in vivo* induction of mutations/ chromosomal aberrations would appear low. The latter conclusion is based on the lack of activity of both drugs in the micronucleus assay, and the fact that mutagenic drug concentrations under *in vitro* conditions exceed C_{max} levels observed in experimental animals by a factor of at least 10-fold.

Carcinogenicity

The sponsor did not perform carcinogenicity testing on the oxycodone:naloxone combination, and there appear to be no published studies on the carcinogenicity of oxycodone. The opioids codeine and oxymorphone (a product of oxycodone metabolism), which are structurally similar to oxycodone, have been shown to be non-carcinogenic in rats and mice. The sponsor did, however, submit studies examining the carcinogenicity of naloxone in rats. Dietary dosing was performed for 2 years at levels up to 100 mg/kg/day (exposure ratio ~300; but see caveats regarding this figure under *Repeat-dose toxicity*). Necropsy results indicated no statistically significant dose-response trends in tumour rates or significant increases in tumour incidence for either male or female rats. The results suggested that dietary administration of naloxone to rats for up to two years was not carcinogenic.

Reproductive and developmental toxicity

All reproductive and developmental stages (that is, fertility and early embryonic development, embryo-fetal development, pre- and postnatal development) were examined for possible effects of naloxone or oxycodone dosing. All studies were performed with the individual drugs and not with the oxycodone:naloxone combination. The sponsor suggested that: "the reproductive and developmental toxicity of the combination would be expected to resemble that of oxycodone." The latter is probably a reasonable expectation given the low systemic levels of naloxone.

The species examined (rat and rabbit), the number of animals per group, the timing and duration of treatment, and the drug doses used, were appropriate. These studies conformed to GLP standards.

Relative exposure

The reproductive and developmental toxicity studies did not include measurements of blood plasma levels of oxycodone, naloxone, or their metabolites. They were, however, performed over similar dose ranges to those used in the pharmacokinetic studies. This allowed the assignment of approximate exposure ratios for the rat studies. Approximate values could not be given for the rabbit studies as there were no pharmacokinetic results to compare with.

Reproductive and developmental studies

Oxycodone

Daily oral dosing with oxycodone of male rats from 28 days prior to mating or female rats from 14 days prior to mating until 7 days *post coitum* produced clinical signs such as chewing on limbs, but had no effect on mating performance, fertility, or early embryonic development. A NOAEL for F_0 rats exposed to oxycodone of less than 0.5 mg/kg/day (exposure ratio < 0.01) and a NOEL for F_0 fertility and F_1 early embryonic development of 8 mg/kg/day (exposure ratio ~ 0.1) were indicated. Possible effects on embryo-fetal development were studied using mated female rats dosed with oxycodone by oral gavage from gestation day 6 (G6) through G15 and euthanised on G20 for necropsy and examination of fetuses. Adverse clinical signs and reduced body weight gain were seen in dams dosed at 3.6 or 7.2 mg/kg/day, however, these doses had no effect on various reproductive parameters, on fetal body weights, or on levels of fetal malformations and developmental variations. NOAELs for maternal toxicity of 1.8 mg/kg/day (exposure ratio ~ 0.03) and for developmental toxicity of 7.2 mg/kg/day (exposure ratio ~ 0.2) were indicated. It was concluded that oxycodone is non-teratogenic in rats at doses up to and including 7.2 mg/kg/day.

Possible embryofetal toxicity was also studied using pregnant rabbits orally dosed with oxycodone at up to 112 mg/kg/day from G6 through G18 and euthanised on G29. Maternal toxicity was noted in the higher dose groups as evidenced by decreased weight gain and decreased activity. There were, however, no observations at necropsy indicative of drug toxicity and there were no effects noted on embryofetal development parameters such as mean numbers of live conceptuses and mean

fetal weight. There were also no statistically significant differences in the incidence of external, visceral, or skeletal malformations between control and drug-dosed groups. There were, however, two statistically significant differences in the incidence of skeletal developmental variations between control and dosed groups. Presacral vertebrae and extra rib variations were increased in 22 and 112 mg/kg/day and in 4.5, 22 and 112 mg/kg/day groups, respectively. The sponsor suggested that the first variation may be related to the maternal toxicity (that is, not directly related to drug dosing) seen at these drug doses, and that the apparently elevated values for the second variation were within historical control ranges. The historical control range data presented by the Middle Atlantic Reproduction and Teratology Association (MARTA) and the Midwest Teratology Association (MTA) (1996) for New Zealand White (NZW) rabbits indicate a fetal incidence for extra ribs of 8.8 ± 17.1% (mean ± standard deviation[SD]) and with a maximum recorded incidence of 67.1%. Accordingly, the values seen in the sponsor's study (45% at 4.5 mg/kg/day and 49% at 112 mg/kg/day) are unusually high and probably indicative of maternal toxicity. Sponsor-suggested NOAELs were 4.5 mg/kg/day for pregnant rabbits and at least 112 mg/kg/day for developmental toxicity.

Possible effects on prenatal and postnatal development were examined using pregnant rats dosed from G6 through lactation day 21 or 23 at 0.5, 2 or 6 mg/kg/day. Females from each dosed group showed expected clinical signs such as chewing on limbs, as well as decreased weight gain in high dose (HD) animals. There were no noteworthy findings, except for a small increase in the duration of gestation in moderate dose (MD) and HD animals (however, the values were within the historical control range). F_1 animals from HD dams showed lower body weights from days 4 to 35 *post partum*, however, there were no other noteworthy findings from this generation. There were no treatment-related effects on F_2 generation viability, clinical observations and body weights. Suggested values for NOAEL for rat exposure during gestation and lactation was <0.5 mg/kg/day (exposure ratio <0.01), and for NOELs for F_1 and F_2 generations were 2 (exposure ratio ~0.06) and ≥ 6 mg/kg/day (exposure ratio ~0.2), respectively.

Naloxone

Male rats were orally dosed for 60 days with naloxone up to 800 mg/kg/day, and females were dosed for 14 days before mating with animals given the same daily dose. Dosing was continued until the day before necropsy (G13 or day 21 *post partum*). There were no apparent dosing-related effects on male or female mating performance nor on reproductive parameters such as mean numbers of corpora lutea and fetal body weights. There were also no effects of naloxone dosing on length of gestation, parturition, nursing performance, or incidence of congenital malformations. There were no statistically significant differences in body weight and development rate between control and drug-dosed pups, although there was a trend towards a lowering of body weight and a slight slowing of development in dosed animals. F_1 animals from control and drug-dosed parents showed no significant differences in learning ability, ophthalmoscopy, auditory function tests, fertility and mating performance, and pregnancy and lactation data. No adverse effects of drug dosing on the F_2 generation were seen. The NOAEL was 50 mg/kg/day (exposure ratio *ca* 100-150) for F_0 males and females and 800 mg/kg/day (exposure ratio >400) for fertility and reproductive performance. Based on the slight developmental retardation of HD pups, the NOAEL for F_1 pups was considered to be 200 mg/kg/day (exposure ratio >400).

Possible embryo-fetal toxicity was examined using pregnant rats dosed from G6 through G15 with naloxone up to 800 mg/kg/day and euthanised on G20 for necropsy and fetal examination. HD animals showed excess salivation, deficit in weight gain, and, after the first dose only, tremors and convulsions. One HD animal (n = 24) died after convulsion. Some MD animals showed occasional excess salivation after dosing, and there was some deficit in weight gain in this group. There were no treatment-related abnormalities at necropsy and no evidence of embryolethality, teratogenicity,

or embryonic growth retardation. Indicated NOAELs were 50 mg/kg/day (exposure ratio about 100-150) for dams and >800 mg/kg/day (exposure ratio >400) for fetuses.

Embryo-fetal toxicity was also examined in pregnant rabbits orally dosed with naloxone up to 400 mg/kg/day from G6 to G18 inclusive. Dams were sacrificed and necropsied on G28 and conceptuses were examined for malformations. Low dose (LD) and MD dams showed no clinical signs after dosing, however, HD animals showed increased respiration during dosing and two had convulsions resulting in one dying and the other aborting. There were no significant differences in bodyweight gain between controls and the dosed groups. Maternal necropsy showed that about 40% of MD and 25% of HD animals had inflammation and/or erosion of the stomach mucosa. As control animals showed similar lesions, albeit at a lower incidence, the study authors suggested that this finding was not attributable to naloxone. There was no statistically significant effect of naloxone dosing on various fetal parameters. Similarly, no effect of naloxone dosing on fetal malformation incidence was noted. It was concluded that the NOAEL for maternal toxicity is 100 mg/kg/day and for developmental toxicity is >400 mg/kg/day.

A second rat study of possible naloxone effects on prenatal and postnatal development involved oral dosing up to 800 mg/kg/day from G15 to day 20 *post partum* inclusive, with both dams and pups sacrificed and necropsied on day 21 *post partum*. There were significant differences in bodyweight gain between controls and the MD and HD groups, however, there was no effect at any dose level on the duration of pregnancy or parturition and no evidence of treatment-related abnormalities in dams and pups. The HD group showed a higher incidence of pup mortality which was attributed to the poorer clinical condition of their dams. Nevertheless, development of surviving offspring in all dosed groups was normal as assessed by time of ear and eye opening and the presence of startle and righting reflex. It was concluded that the NOAEL for maternal toxicity is 50 mg/kg/day and for developmental toxicity is >800 mg/kg/day.

Paediatric use

Targin tablets are not intended for use in children. Paediatric studies have not been performed and a paediatric development program is not proposed at this time.

Antigenicity

The possible antigenicity of oxycodone or naloxone was not examined.

Phototoxicity and local tolerance

Possible phototoxic potential of oxycodone and naloxone was not examined, but would seem unlikely given the relatively rapid metabolism and excretion of these compounds. Repeat intranasal administration of naloxone in male rats was well tolerated and did not cause local irritation at the doses tested.

Nonclinical Summary and Conclusions

In vitro studies by the sponsor confirmed that oxycodone has moderate affinity for human μ-opioid receptors and stimulates G protein association and GTP binding, but has low affinity for κ- and δ-opioid receptors. Two oxycodone metabolites, oxymorphone and noroxymorphone, were shown to have significantly higher affinity for μ-opioid receptors than the parent compound. Naloxone and its metabolites 6α/β-naloxol and noroxymorphone showed high affinity binding for human μ-opioid receptors, however, naloxone and 6α/β-naloxol did not stimulate functional activity (that is, GTP binding).

Oxycodone, naloxone and their metabolites showed only weak to moderate ability to inhibit the voltage-gated potassium channel at supra-physiological concentrations suggesting that these drugs have a low potential for cardiotoxicity.

Specific safety pharmacology studies were not performed because of the long history of clinical use for both oxycodone and naloxone. Animal toxicology studies performed by the sponsor did not show toxicologically-relevant changes in ECG or blood pressure.

Pharmacokinetic studies of rats and dogs orally dosed with oxycodone and/or naloxone showed: rapid uptake from the gut with T_{max} times generally around 0.5 h; noroxycodone (a weak binder of the μ-opioid receptor) was clearly the major metabolite of oxycodone whilst much lower levels of the strong opioid receptor binders, oxymorphone and noroxymorphone, were produced; naloxone-3-glucuronide (very weak binder of the μ-opioid receptor) was the major metabolite of naloxone, with other metabolites present at much lower levels; linear pharmacokinetics for both oxycodone and naloxone; similar pharmacokinetics in both sexes for dogs, but male rats metabolised both oxycodone and naloxone more rapidly than females; oxycodone does not interfere with the metabolism of naloxone and *vice versa*; after repeated dosing for weeks or months there was little evidence for accumulation of oxycodone or naloxone in dogs and evidence of modest accumulation (up to about 2x) in rats; and IV-infused naloxone has a half-life in dogs of *ca* 17-56 min.

Oxycodone metabolism occurs primarily in the liver and can involve at least five separate pathways. The three most important of these metabolic pathways are: (1) 6-keto reduction to 6α/β-oxycodol; (2) *O*-demethylation to oxymorphone primarily catalysed by CYP2D6; and (3) *N*-demethylation to noroxycodone primarily catalysed by CYP3A4. Oxymorphone can then undergo glucuronidation, whilst noroxycodone can undergo glucuronidation or conversion (via CYP2D6) to noroxymorphone. Naloxone was metabolised in liver through at least three separate pathways: (1) 6-keto reduction to 6α/β-naloxol catalysed by 3α-hydroxysteroid dehydrogenase; (2) glucuronidation to naloxone-3-glucuronide catalysed by UDP-glucuronosyltransferase; and (3) *N*-deallylation to noroxymorphone primarily catalysed by CYP3A4. Metabolic pathways/metabolites were similar in tested species and humans.

Excretion and tissue distribution studies were not performed by the sponsor. Literature studies suggest that the various metabolic products of oxycodone and naloxone are excreted in urine and faeces, with most drug eliminated within 2-3 days of dosing.

Oxycodone and naloxone (alone or in combination) did not inhibit major drug-metabolising cytochrome P450 enzymes from human liver microsomal preparations, suggesting that there is little likelihood for their interference with the CYP metabolism of other drugs.

Studies using *in vitro* cultured normal human hepatocytes suggested that therapeutic levels of naltrexone, paracetamol or acetylsalicylic acid would have little effect on the metabolism of oxycodone and naloxone.

Repeat-dose toxicity studies were conducted in rats (oxycodone up to 3 months, naloxone up to 2 years, and oxycodone:naloxone up to 3 months) and dogs (oxycodone up to 3 months, naloxone up to 9 months, and oxycodone:naloxone up to 3 months). Exposure ratios (blood plasma oxycodone or naloxone levels relative to levels in humans given recommended maximum dose) were up to 1-2 for oxycodone and up to about 300 for naloxone. Relative oxycodone exposures were limited by clinical toxicity.

In both rats and dogs, clinical signs were those classically associated with opioid intake (for example, appetite suppression). Clinical signs resolved quickly after cessation of dosing and there were no toxicologically significant findings in dosed animals.

In vitro mutation and chromosomal aberration assays suggested that oxycodone, in the presence of metabolic activation mix, has weak ability to induce clastogenic events. There was, however, no significant increase in the frequency of micronucleated erythrocytes in mice given a single oral dose of oxycodone. Relatively high concentrations of naloxone induced mutations and chromosomal

aberrations in *in vitro* cultured cells, however, they produced no response in the micronucleus assay. Based on the overall weight of evidence, the genotoxic liability of the product is low.

Neither the oxycodone:naloxone combination nor oxycodone alone was tested for carcinogenicity. Naloxone alone, however, produced no significant increase in tumour incidence in rats that received the drug for 2 years in their diet.

Dosing with oxycodone or naloxone alone had no significant effects on mating performance, fertility, fetal and embryonic development, and prenatal and postnatal development in rats or rabbits. There was no indication that oxycodone or naloxone might be teratogens in rats or rabbits. Oxycodone NOAELs for developmental toxicity of 7.2 mg/kg/day (exposure ratio ~ 0.2) and at least 112 mg/kg/day were estimated for rats and rabbits, respectively. For naloxone, estimated NOAELs for developmental toxicity in rats and rabbits were >800 and >400 mg/kg/day, respectively.

No significant adverse properties of oxycodone/naloxone dosing were demonstrated by the sponsor's investigations. Studies in key areas indicated: a lack of toxicologically significant findings and a quick resolution of clinical signs after repeat dosing with oxycodone/naloxone in rats and dogs; the genotoxic potential of both drugs under *in vivo* dosing conditions is low; naloxone is not carcinogenic in rats; there is no evidence that oxycodone or naloxone are teratogens in rats or rabbits.

There are no nonclinical objections to the registration of Targin for the treatment of moderate to severe chronic pain, as proposed by the sponsor. The toxicological profiles of the individual components (oxycodone, naloxone) are well known from previous evaluations, and both are registered in other products.

IV. Clinical Findings

Introduction

The clinical development programme for OXN PR comprised the following:

- three pivotal Phase III clinical studies (OXN3001, OXN3006, OXN3401) conducted in patients with non-malignant pain
- one dose-finding study (OXN2401) in patients with chronic pain of tumour and non-tumour origin, and
- 15 clinical pharmacology studies (OXN1401, OXN1403, OXN1001, OXN1003, OXN1004, OXN1008, OXN1009, OXN1011, OXN1016, OXN1013, OXN1018), including studies in the elderly (OXN1017), in hepatic (OXN1006) and renal (OXN1007) impairment, as well as in methadone-stabilised addicts (OXN1402).

This dossier included data from all 19 clinical studies. The three Phase III studies were nominated by the sponsor as pivotal for demonstrating efficacy in terms of both maintained analgesia and improved bowel function. Long-term data were provided from the Extension Phase of study OXN3401 (OXN3401S). Additional information presented in the submission included 1) a validation of Bowel Function Index (BFI), which was the primary endpoint in the pivotal bowel function studies (OXN3001 and OXN3006), 2) a meta-analysis (OXN9001) of studies OXN3001 and OXN3006, and 3) an observational, post-marketing surveillance study (OXN9002).

All studies were conducted according to current Good Clinical Practice (GCP) standards.

Pharmacokinetics

Pharmacokinetic data were provided from 10 single dose studies with OXN PR (OXN1403, OXN1003, OXN1004, OXN1006, OXN1007, OXN1008, OXN1009, OXN1016, OXN1013, OXN1018), 2 multiple dose studies with OXN PR (OXN1011, OXN1017), and one study

investigating the absolute bioavailability of intranasally and sublingually administered naloxone compared with intravenously administered naloxone (OXN1001).

Biopharmaceutic Studies and Studies Investigating Effect of Food

Study OXN1403 was an open-label, single-dose, 4-treatment, 4-period, randomised crossover study in healthy subjects. The objectives were:

- to evaluate PK and bioavailability parameters of oxycodone prolonged release (PR) and naloxone PR and their main metabolites when administered as a fixed combination tablet
- to assess the interchangeability between the 3 different strengths of the fixed combination
- to compare the fixed combination with marketed Oxygesic given together with a naloxone PR tablet.

Results

Study OXN1403 was the most definitive of the Phase I studies in terms of defining the bioavailability and bioequivalence of the range of OXN PR strengths. Results are illustrated in Figures 1 and 2.

The mean plasma oxycodone concentration-time curves for 2 x Oxygesic 20 mg and with 2 x naloxone PR 10 mg and the fixed combination tablets were almost super-imposable. Similarly, the mean plasma naloxone-3-glucuronide concentration-time curves for 2 x Oxygesic 20 mg and with 2 x naloxone PR 10 mg and the fixed combination tablets were almost super-imposable. Study OXN1403 results supported that the fixed combination tablets were bioequivalent to Oxygesic given together with naloxone PR tablet.

Figure 1: Study OXN1403 - Mean Plasma Concentration-time Curves for Oxycodone Over Time by Treatment - Full Analysis Population for Pharmacokinetics

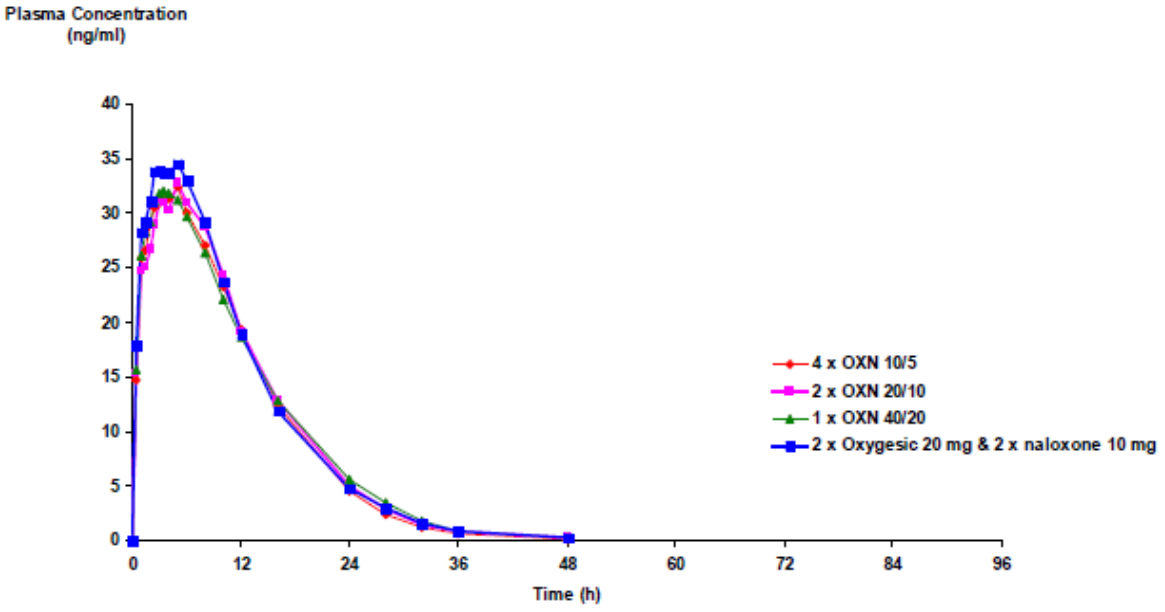
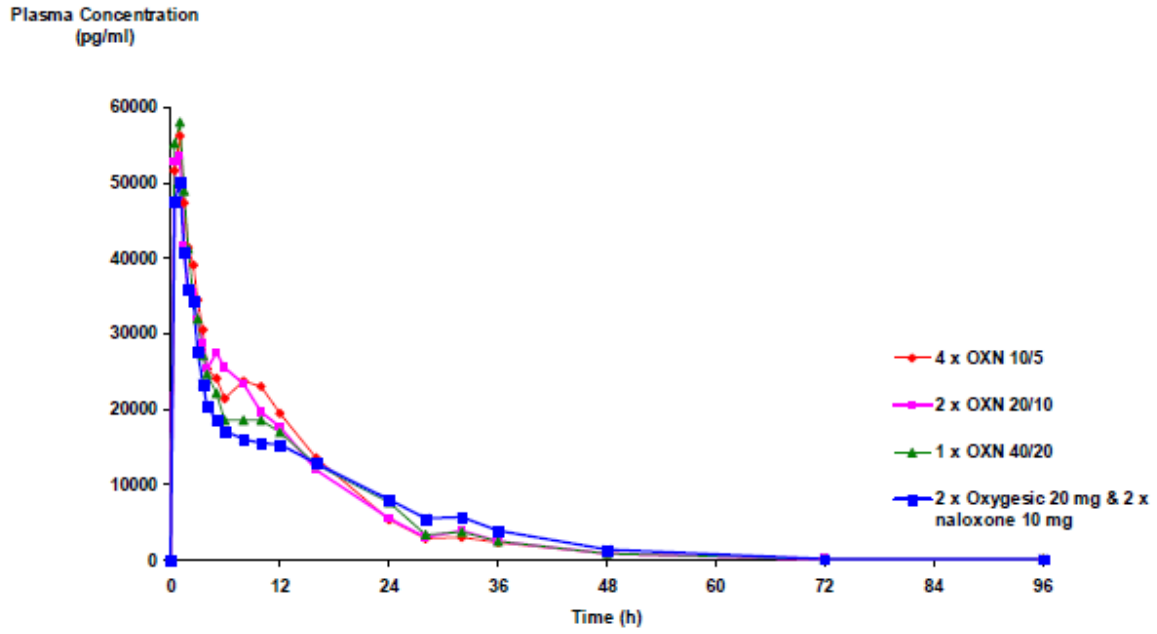


Figure 2: Study OXN1403 - Mean Plasma Concentration - time Curves for Naloxone-3-glucuronide Overtime by Treatment - Full Analysis Population for Pharmacokinetics



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Study 1011 was an open-label, single centre, multiple-dose, steady state, 3-treatment, 3-period, randomised crossover study in healthy male and female subjects. The three different treatments were:

- OXN40/20 mg PR twice daily (bd) over 7 dosages
- Oxygesic 40 mg, bd over 7 dosages
- Naloxone 20 (2 x 10) mg PR tablets, bd over 7 dosages.

In addition to the above mentioned treatments the subjects also received naltrexone tablets to prevent opioid-related side effects. The objectives of this study were to determine the bioequivalence of oxycodone and naloxone- 3-glucuronide from OXN40/20 mg PR tablet compared with oxycodone from an oxycodone PR tablet 40 mg, and naloxone-3-glucuronide from naloxone PR tablets 2 x 10 mg. This study was also discussed in Section II.

Results

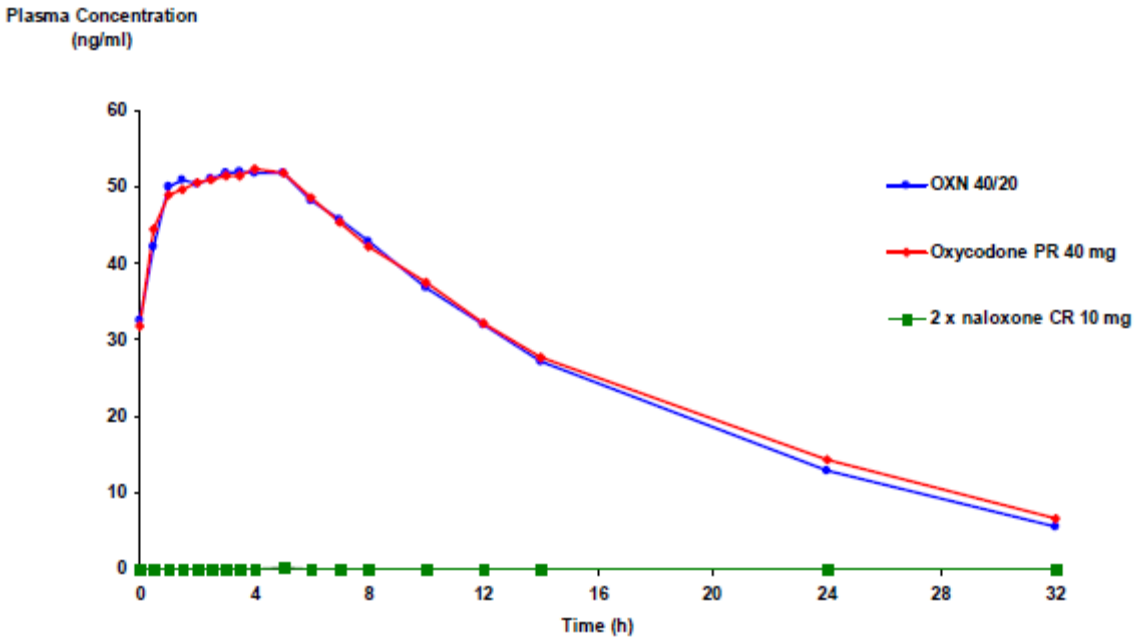
Examination of the mean trough concentrations for oxycodone and naloxone-3-glucuronide revealed that steady state conditions had been attained at the fourth day.

Oxycodone Results

Figure 3 presents the mean plasma concentrations of oxycodone following twice daily administration. In terms of oxycodone, the results of the study demonstrated that OXN40/20 mg PR was bioequivalent to oxycodone PR tablets in terms of the area under the plasma-concentration time course profile from time 0 (dosing) to the last quantifiable concentration (AUC_t), maximum observed concentration at steady state (C_{maxss}) and minimum observed concentration at steady state (C_{minss}). The mean half-life of oxycodone was similar for the oxycodone PR tablet (6.27 hours) and for OXN40/20mg PR (5.33 hours). Both values were similar to previous data collected on the OXN PR combination product and on oxycodone given as a single prolonged-release entity. Results

supported that the pharmacokinetics of oxycodone were not influenced by the co-administration of naloxone.

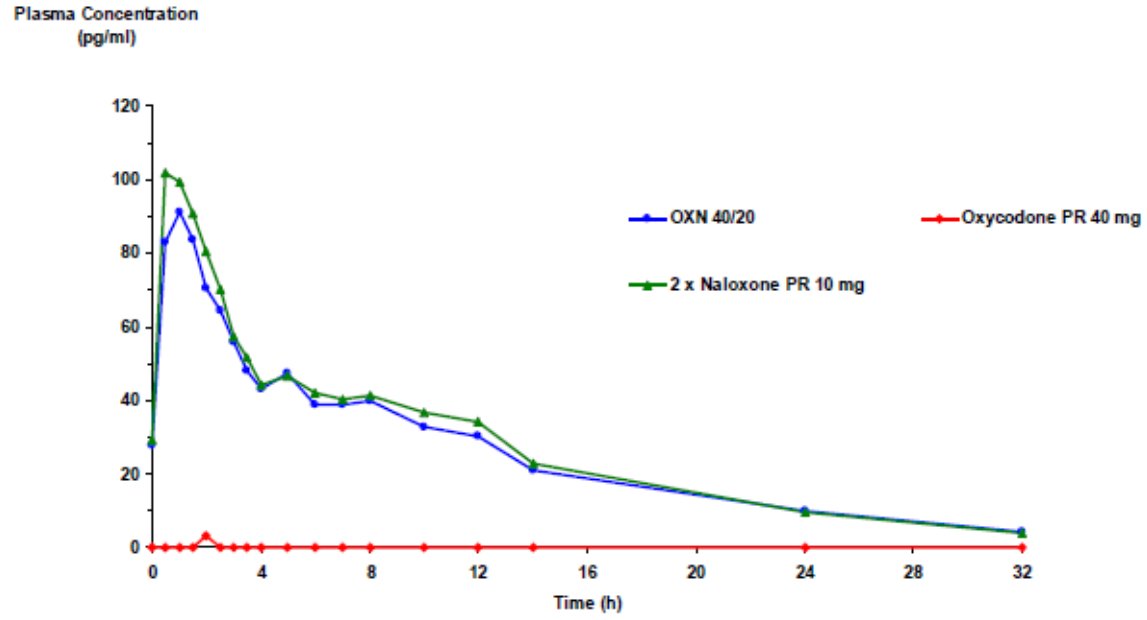
Figure 3: Study OXN1011 - Mean Oxycodone Plasma Concentration Following Twice Daily Administration of OXN40/20 mg PR tablets, 40 mg Oxycodone PR tablets or 20 mg Naloxone PR Tablets (mislabelled on the Figure)



Naloxone-3-glucuronide Results

Figure 4 presents the mean plasma concentrations of naloxone-3-glucuronide oxycodone following twice daily administration. OXN40/20 mg PR was shown to be bioequivalent to 20 (2 x 10) mg naloxone PR tablets in terms of AUC_t and C_{maxss} of naloxone-3-glucuronide; however the C_{minss} ratio did not meet the criteria for bioequivalence.

Figure 4: Study OXN1011 - Mean Naloxone-3-glucuronide Plasma Concentration Following Twice Daily Administration of OXN40/20 mg PR, 40 mg Oxycodone PR or 20 mg Naloxone PR Tablets



Study OXN1018 was an open-label, single-dose, 4-treatment, 4-period, randomised crossover study in healthy male and female subjects. The objectives of this study were to determine the bioequivalence of OXN5/2.5 mg PR with oxycodone prolonged release (OxyPR) tablet 5 mg and also to assess the effect of food on the bioavailability of oxycodone and naloxone from OXN5/2.5 mg PR. The 4 treatments were as follows:

- OXN5/2.5 mg PR, fasted
- OXN5/2.5 mg PR, fed
- oxycodone immediate release (OxyIR) liquid 5 mg + naloxone injection 2.5 mg
- OxyPR tablet 5 mg, fasted.

Study OXN1018 was also performed to assess the effect of food on the PK parameters of oxycodone and naloxone (naloxone-3-glucuronide) from OXN5/2.5 mg PR tablets. This study was also discussed in Section II.

Results

Oxycodone and Naloxone-3-glucuronide Results

The mean oxycodone plasma concentrations are illustrated in Figure 5 and the mean naloxone-3-glucuronide concentrations are illustrated in Figure 6. The study showed that OXN5/2.5 mg PR and OxyPR tablet 5 mg are bioequivalent for the main analyte oxycodone. Administration of OXN5/2.5 mg PR after a high fat breakfast had no effect on the bioavailability of oxycodone or naloxone-3-glucuronide, compared with administering OXN5/2.5 mg PR in a fasted state. The presence of food increased the mean C_{max} value for oxycodone by 42% which is consistent with results noted previously for OXN PR tablets and oxycodone PR tablets.

Figure 5: Study OXN1018 - Mean Plasma Concentration-time Curves for Oxycodone Over Time by Treatment - Full Analysis Population for Pharmacokinetics

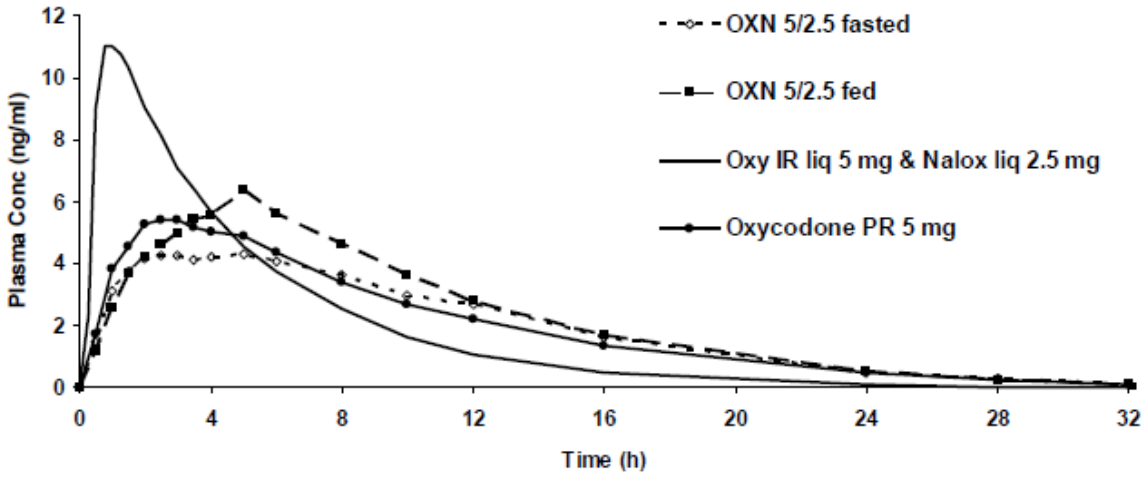
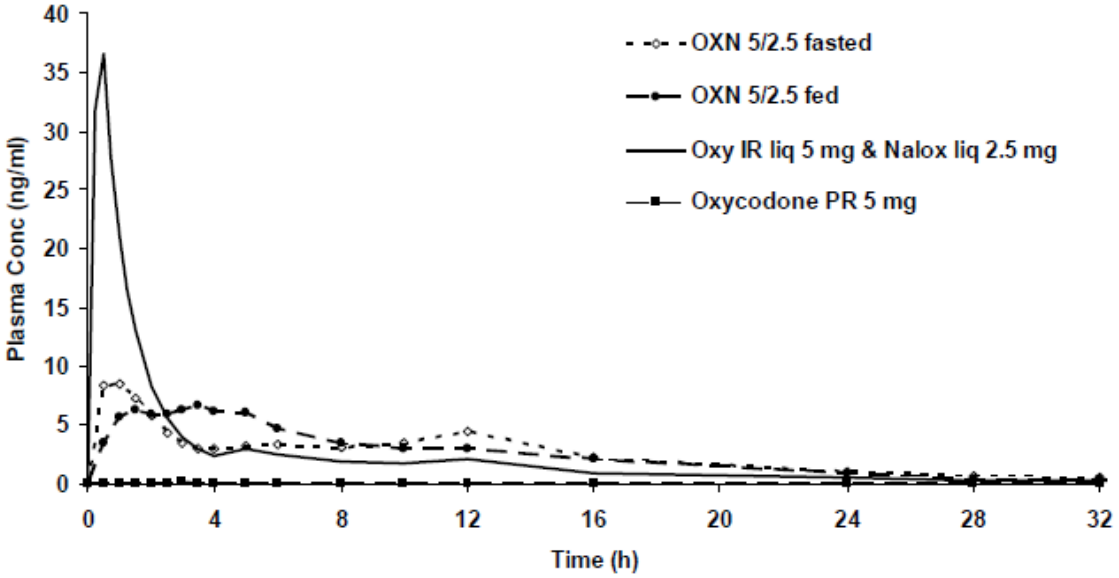


Figure 6: Study OXN1018 – Mean Plasma Concentration-time Curves for Naloxone-3-glucuronide Over Time by Treatment - Full Analysis Population for Pharmacokinetics



Results showed that administering OXN5/2.5 mg PR after a high fat breakfast had no effect on the bioavailability of oxycodone or naloxone-3-glucuronide, compared with administering OXN5/2.5 mg PR in a fasted state. The PK parameters also demonstrated that the presence of food increased the mean C_{max} value for oxycodone by 42%, which is consistent with results observed in other studies described below.

Study OXN1003 was a pilot, open-label, single-dose, randomised, 4-treatment, 4-period crossover study in healthy subjects. The objective was to investigate the effect of a high-fat breakfast on the bioavailability of oxycodone and naloxone-3-glucuronide when administered as a fixed combination prolonged release tablet.

Results

Results of study OXN1003 demonstrated that administering OXN40/20 mg PR and OXN10/5 mg PR after a high fat breakfast had no effect on the bioavailability of oxycodone or naloxone-3-glucuronide, compared with administering OXN40/20 mg PR and OXN10/5 mg PR in a fasted state. The presence of food did not alter the mean C_{max} value for naloxone-3-glucuronide. There was a slightly increased mean C_{max} value for oxycodone; however this was not considered to be clinically significant.

Study OXN1008 was an open-label, single-dose, 3-treatment, 3-period, randomised crossover study in healthy male and female subjects. Each subject received a single dose of the following treatments:

- OXN40/20 mg PR in a fed state,
- OXN40/20 mg PR in a fasted state
- 20 mg Oxycodone IR (OxyIR) plus 10 mg naloxone IR solution.

A reduced dosage of OxyIR was considered appropriate to ensure an acceptable tolerability profile. Naltrexone was also administered to each of the treatment groups to minimise opioid related side effects such as nausea or vomiting.

The primary objective of the study was to assess the effect of food on the bioavailability of oxycodone and naloxone (or surrogate of naloxone) from OXN40/20 mg PR. A further objective

was to compare the pharmacokinetics of oxycodone and naloxone (or surrogate of naloxone) from OXN40/20 mg PR with the pharmacokinetics from the open combination of oxycodone hydrochloride immediate release liquid 20 mg and naloxone hydrochloride liquid 10 mg. This study was also discussed in Section II.

Results

Overall the results showed that the availabilities of oxycodone and naloxone-3-glucuronide from OXN40/20 mg PR were not affected by food; however food did increase the mean observed C_{max} values of oxycodone from OXN40/20 mg PR by 28%, which is consistent with data from other studies for oxycodone given as a single entity. The naloxone-3-glucuronide C_{max} values were unaffected by food.

Study OXN1009 was an open-label, single-dose, 3-treatment, 3- period, randomised crossover study in healthy male and female subjects. Each subject received a single dose of the following treatments:

- OXN10/5 mg PR in a fasted state
- OXN10/5 mg PR in a fed state
- 10 mg OxyIR + 5 mg naloxone IR solution.

The primary objective of this study was to assess the effect of food on the bioavailability of oxycodone and naloxone (or surrogate of naloxone) from OXN10/5 mg PR. Another objective was to compare the pharmacokinetics of oxycodone and naloxone (or surrogate of naloxone) from OXN10/5 mg PR with oxycodone immediate release liquid 10 mg and naloxone liquid 5 mg.

Results

The administration of OXN10/5 mg PR after a high-fat breakfast had no effect on the bioavailability of oxycodone or naloxone-3-glucuronide compared with OXN10/5 mg PR in a fasted state. The presence of food did not alter the mean C_{max} value for naloxone-3-glucuronide, and increased the mean C_{max} value for oxycodone by 27%, which is consistent with results seen in study OXN1008. The effects were considered not to be of clinical significance.

Influence of Scale-up in Batch Size

Study OXN1004 was an open-label, single-dose, randomised, 4-treatment, 4-period crossover study in healthy subjects. The objectives were to establish the bioequivalence of both oxycodone and naloxone (or surrogate) from a fixed combination PR tablet OXN10/5 mg PR and OXN40/20 mg PR manufactured as a small-scale batch with OXN10/5 mg PR and OXN40/20 mg PR manufactured as a large-scale batch, by comparing the AUC ratio and C_{max} ratio as primary measures.

The study was terminated after period 1 due to the high incidence of nausea and vomiting. The adverse effects (AEs) were evenly distributed across all four treatment groups. The AE profile observed in this study was consistent with what would be expected of a strong opioid. No formal statistical PK analyses were performed as data were gathered for one treatment period only; however the limited descriptive data from the study supported there being no differences between the small laboratory scale and large production scale batches of the same strength OXN PR tablets.

Study OXN1016 was a single-dose, open-label, 5-treatment, 5-period, randomised crossover study in healthy subjects. The different treatments were:

- OXN10/5 mg PR (laboratory-scale batch)
- OXN10/5 mg PR (production-scale batch)
- OXN10/5 mg PR (production-scale batch) + naltrexone
- OXN40/20 mg PR (laboratory-scale batch) + naltrexone

- OXN40/20 mg PR (production-scale batch) + naltrexone.

The primary objectives of this study were to establish the bioequivalence of both oxycodone and naloxone (or surrogate) from OXN10/5 mg PR and OXN40/20 mg PR manufactured as a laboratory-scale batch with OXN10/5 mg PR and OXN40/20 mg PR manufactured as a production-scale batch, by comparing the relative bioavailability (AUC_∞ [the area under the plasma concentration time curve from time zero to infinite time] ratio or AUC_t ratio) and C_{max} ratio as primary measures. An additional objective was to investigate the effect of naltrexone on the pharmacokinetics of oxycodone and naloxone from OXN10/5 mg PR production-scale. This study was also discussed in Section II.

Results

The oxycodone and naloxone-3-glucuronide results confirmed that the scaled up production batches of both OXN10/5 mg PR and OXN40/20 mg PR were bioequivalent to the smaller laboratory-scale batches. The administration of naltrexone did not have any effect on the pharmacokinetics of oxycodone or naloxone-3-glucuronide from OXN10/5 mg PR production-scale. Dose-proportionality between OXN10/5 mg PR and OXN40/20 mg PR production-scale, both administered with naltrexone cover, was confirmed.

Study 1013 was an open-label, single-dose, 4- treatment, 4-period, randomised crossover study in healthy male subjects. Subjects received each of the 4 treatments according to a random allocation schedule with at least a 7-day washout period between each dosing. Subjects received one of the following treatments:

- OXN20/10 mg PR, slow release batch (OXN20/10 mg PR Slow)
- OXN20/10 mg PR medium release batch (OXN20/10 mg PR Medium)
- OXN20/10 mg PR fast release batch (OXN20/10 mg PR Fast)
- OxyIR liquid and naloxone injection (the IR Solution).

The primary objective of study OXN1013 was to obtain PK data from batches of OXN20/10 mg PR with different release rates (slow, medium, fast) to be used in establishing an *in vitro-in vivo* correlation (IVIVC) and to assess the safety of batches of OXN20/10 mg PR with different release rates (slow, medium, fast), when administered in a fasted state to healthy subjects. This study was also discussed in Section II.

Results

As would be expected, OXN20/10 mg PR Slow, Medium and Fast release preparations provided plasma profiles and associated peak plasma concentrations that were in line with those expected from their in vitro dissolution rates.

Study OXN1001 was a single-centre, open-label, randomised investigation in healthy subjects to assess the absolute bioavailability of 8 mg and 16 mg intranasally and 16 mg sublingually administered naloxone compared with 1 mg of intravenously administered naloxone.

There were 4 single-dose, open-label treatments, with a minimum 14-day washout between each treatment. The treatments were naloxone 8 mg and 16 mg administered as 400 µL intranasally (200 µL per nostril) and naloxone 16 mg administered sublingually in a 1 mL solution which was retained under the tongue for 5 minutes. Intravenous naloxone 1 mg administered as a 1 mL bolus served as the reference treatment.

The results from study OXN1001 indicated a substantial level of absorption of naloxone by the intranasal route coupled with a reasonably slow elimination pattern.

In contrast, the mean absolute bioavailability of naloxone when administered by the sublingual route was very low (approximately 2%) compared to the intravenous reference. This is comparable to that recorded previously following oral administration.

Pharmacokinetic Studies in Special Populations

Three Phase I studies were performed in special populations to assess the PK parameters of oxycodone and naloxone from OXN PR under special circumstances. These studies were: OXN1017 (Phase I study in elderly subjects), OXN1006 (Study in patients with varying degree of hepatic impairment), and OXN1007 (Study in patients with varying degree of renal impairment).

Study OXN1017 was an open-label, single-centre, multiple-dose study to compare the steady-state pharmacokinetics of oxycodone, naloxone and their metabolites from OXN10/5 mg PR in healthy elderly subjects (≥65 years) and healthy younger subjects (18 – 45 years). After the screening period (up to 21 days) subjects received OXN10/5 mg PR twice daily. The number of OXN10/5 mg PR intakes was 7 doses in total. Naltrexone was administered to prevent opioid-related side effects like nausea and vomiting.

Results

Oxycodone Results

The availability of oxycodone from OXN10/5 mg PR in the elderly subjects was on average 18% higher than for the younger subjects, and the upper 90% CI was outside the bioequivalence limit. This difference between elderly and younger subjects was more apparent in female subjects (mean increase in AUC_t of 33%) than male subjects (mean increase in AUC_t of 3%), however due to the small number of subjects in the study the apparent difference between male and female should be interpreted with caution.

The increase in oxycodone availability in the elderly seemed to correlate with creatinine clearance. Creatinine clearance is known to decrease with age and it is noticeable that there were differences in creatinine clearance between elderly and younger subjects that were of a similar magnitude to the observed difference in oxycodone bioavailability. Increases were observed in the maximal concentration of oxycodone at steady state (C_{maxss}) (14%) and the minimal concentration at steady state (C_{minss}) (28%) values and neither met the criteria for bioequivalence.

Naloxone Results

The plasma naloxone concentrations were higher in the elderly group, resulting in an increase in bioavailability of naloxone of 82%. The difference between elderly and younger subjects was more apparent in female subjects (mean increase in AUC_t of 135%) than male subjects (mean increase in AUC_t of 36%). However, in contrast to results with oxycodone, the changes in naloxone exposure were much more variable and the confidence intervals were too wide to allow definitive conclusions to be drawn.

In light of the results from study OXN1017 the sponsor recommends that in elderly subjects, the starting dose of OXN PR should be a low one.

Study OXN1006 was an open-label, single-dose, parallel group study to compare the pharmacokinetics of oxycodone and naloxone from OXN10/5 mg PR in patients with varying degrees of hepatic impairment and healthy volunteers and to identify an appropriate dose recommendation for patients with hepatic impairment. Subjects eligible for the study were healthy volunteers and subjects with varying degrees of hepatic impairment based on the Child Pugh Grading where mild = 5-6, moderate = 7-9, and severe = 10-15. After a screening period, (up to 21 days) all subjects received a single dose of OXN10/5 mg PR.

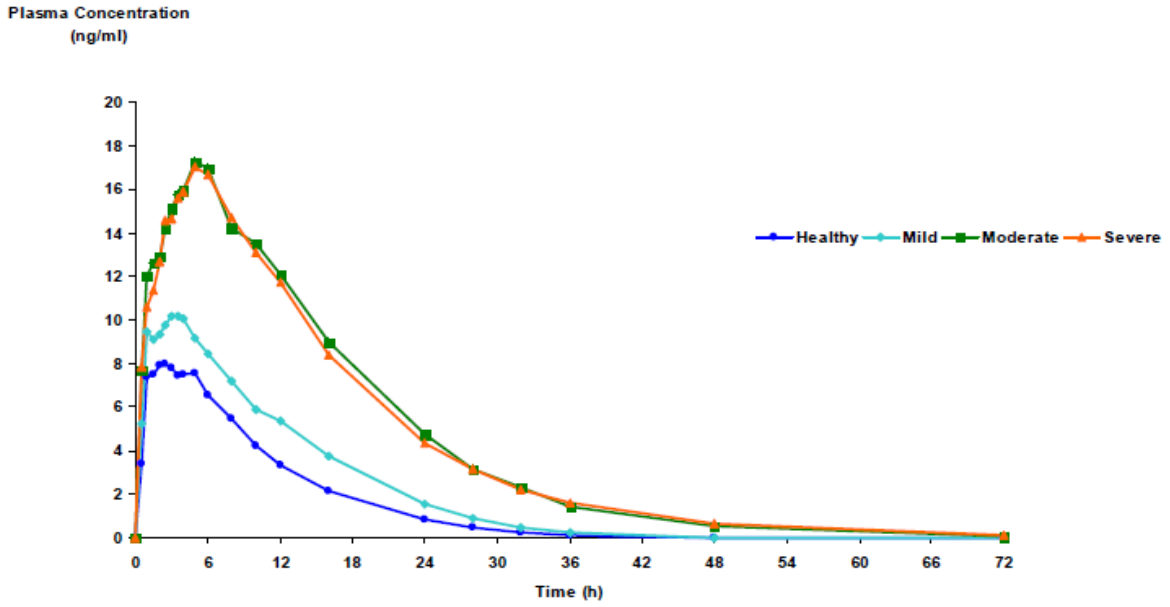
Results

Mean plasma concentration - time curves for oxycodone and naloxone over time by treatment are shown in Figures 7 and 8, respectively. Overall results showed that there was up to a 3-fold increase in the bioavailability of the oxycodone component and a more than 100-fold increase in the bioavailability of the naloxone component of the 10/5 mg dose of OXN PR in the moderate and severe hepatically impaired groups compared with the healthy subject group.

Oxycodone

For AUC_∞ of oxycodone, on average there was an increase to 143% (90% confidence interval (CI): 111, 184), 319% (90% CI: 248, 411) and 310% (90% CI: 241, 398) for mild, moderate and severe hepatically impaired subjects, respectively, compared with healthy volunteers. For C_{max} of oxycodone, on average there was an increase to 120% (90% CI: 99, 144), 201% (90% CI: 166, 242) and 191% (90% CI: 158, 231) for mild, moderate and severe hepatically impaired subjects, respectively, compared with healthy volunteers. For $t_{1/2}$ of oxycodone, on average there was an increase to 108% (90% CI: 70, 146), 176% (90% CI: 138, 215) and 183% (90% CI: 145, 221) for mild, moderate and severe hepatically impaired subjects, respectively, compared with healthy volunteers.

Figure 7: Study OXN1006 - Mean Plasma Concentration - time Curves for Oxycodone Over Time by Treatment - Full Analysis Population for Pharmacokinetics



Naloxone

For AUC_t of naloxone, on average there was an increase to 411% (90% CI: 152, 1112), 11518% (90% CI: 4259, 31149) and 10666% (90% CI: 3944, 28847) for mild, moderate and severe hepatically impaired subjects, respectively, compared with healthy volunteers. For C_{max} of naloxone, on average there was an increase to 193% (90% CI: 115, 324), 5292% (90% CI: 3148, 8896) and 5252% (90% CI: 3124, 8830) for mild, moderate and severe hepatically impaired subjects, respectively, compared with healthy volunteers. Due to insufficient amount of data available $t_{1/2}$ and the corresponding AUC_∞ of naloxone were not calculated. The bioavailability comparisons for naloxone were therefore based on AUC_t values.

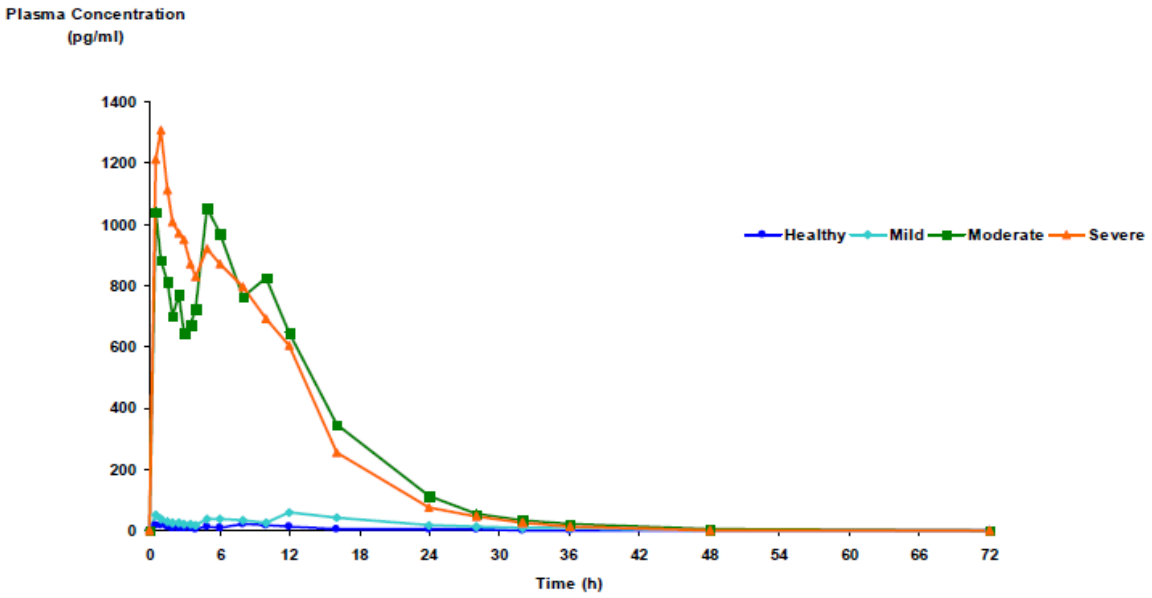
Naloxone-3-glucuronide

For AUC_∞ of naloxone-3-glucuronide, on average there was an increase to 157% (90% CI: 89, 279), 128% (90% CI: 72, 227) and 125% (90% CI: 71, 222) for mild, moderate and severe

hepatically impaired subjects, respectively, compared with healthy volunteers. For C_{max} of naloxone-3-glucuronide, on average there was an increase to 141% (90% CI (CI): 100, 197), 118% (90% CI: 84, 166) and a decrease to 98% (90% CI: 70, 137) for mild, moderate and severe hepatically impaired subjects, respectively, compared with healthy volunteers. For $t_{1/2}$ of naloxone-3-glucuronide, on average there was an increase to 117% (90% CI: 72, 161), a decrease to 77% (90% CI: 32, 121) and a decrease to 94% (90% CI: 49, 139) for mild, moderate and severe hepatically impaired subjects, respectively, compared with healthy volunteers.

In light of the results from study OXN1006 the sponsor recommends that moderate to severe hepatic impairment is a contraindication to use of the fixed combination.

Figure 8: Study OXN1006 - Mean Plasma Concentration - time Curves for Naloxone Over Time by Treatment - Full Analysis Population for Pharmacokinetics



Study OXN1007 was an open-label, single-dose, parallel-group study to compare the pharmacokinetics of oxycodone, naloxone and their metabolites from OXN10/5 mg PR in patients with varying degrees of renal impairment and healthy volunteers, and to identify an appropriate dose recommendation for patients with renal impairment. The study aimed to include renal impairment patients in each renal impairment group (mild, moderate, and severe) based on Creatinine Clearance values. After a screening period (up to 21 days) every subject received a single dose of OXN10/5 mg PR.

Results

Mean plasma concentration - time curves for oxycodone and naloxone over time by treatment are shown in Figures 9 and 10, respectively.

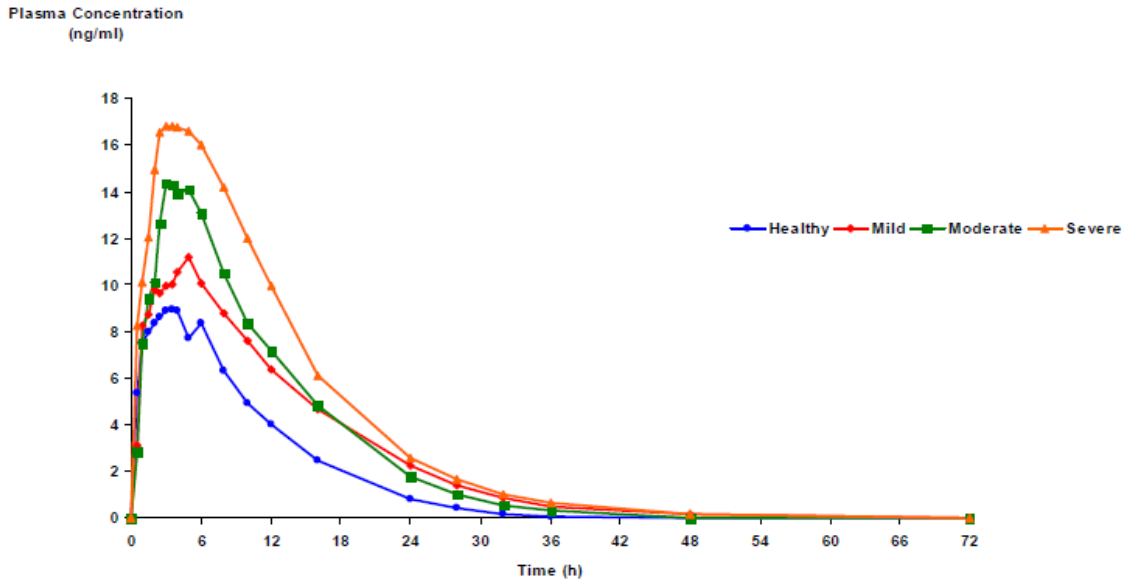
Oxycodone

For AUC_{∞} of oxycodone, on average there was an increase to 153% (90% CI: 130, 182), 166% (90% CI: 140, 196) and 224% (90% CI: 190, 266) for mild, moderate and severe renally impaired subjects, respectively, compared with healthy volunteers.

For C_{max} of oxycodone, on average there was an increase to 110% (90% CI: 94, 129), 135% (90% CI: 115, 159) and 167% (90% CI: 142, 196) for mild, moderate and severe renally impaired subjects, respectively, compared with healthy volunteers.

For $t_{1/2}$ of oxycodone, on average there was an increase to 149%, 123% and 142% for mild, moderate and severe renally impaired subjects, respectively, compared with healthy volunteers.

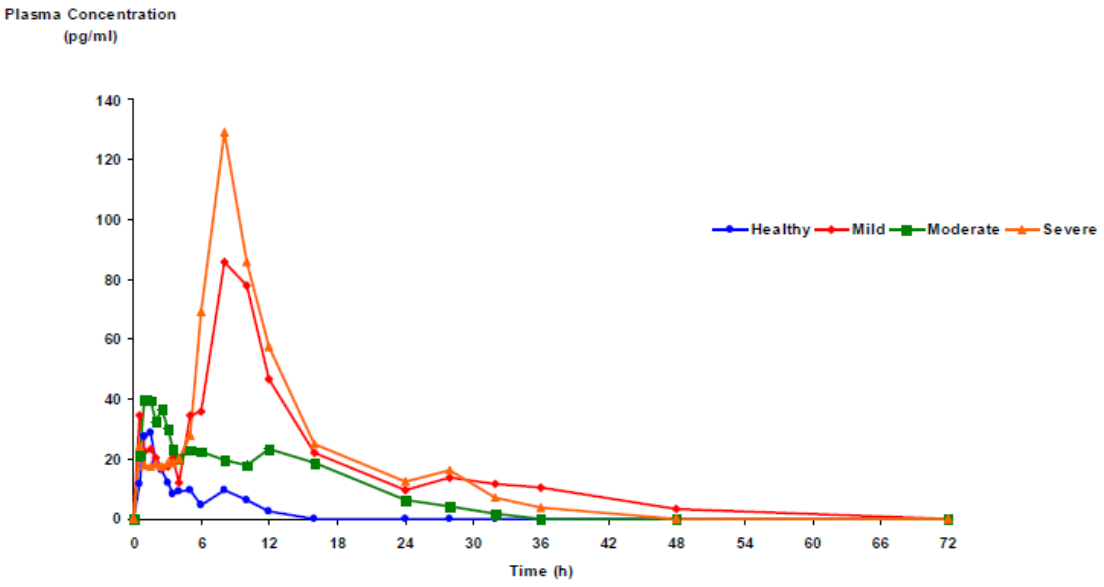
Figure 9: Study OXN1007 - Mean Plasma Concentration - time Curves for Oxycodone Over Time by Treatment - Full Analysis Population for Pharmacokinetics



Naloxone

For AUC_t of naloxone, on average there was an increase to 2850% (90% CI: 369, 22042), 3910% (90% CI: 506, 30243) and 7612% (90% CI: 984, 58871) for mild, moderate and severe renally impaired subjects, respectively, compared with healthy volunteers. For C_{max} of naloxone, on average there was an increase to 1076% (90% CI: 154, 7502), 858% (90% CI: 123, 5981) and 1675% (90% CI: 240, 11676) for mild, moderate and severe renally impaired subjects, respectively, compared with healthy volunteers.

Figure 10: Study OXN1007- Mean Plasma Concentration - time Curves for Naloxone Over Time by Treatment - Full Analysis Population for Pharmacokinetics



Due to insufficient amount of data available the terminal phase half-life ($t_{1/2}$) and the corresponding AUC_∞ of naloxone were not calculated. The bioavailability comparisons for naloxone were therefore based on AUC_t values. The ratios may have been influenced by the inability to fully characterize the naloxone plasma profiles for the healthy subjects.

Naloxone-3-glucuronide

For AUC_∞ of naloxone-3-glucuronide, on average there was an increase to 220% (90% CI: 148, 327), 370% (90% CI: 249, 550) and 525% (90% CI: 354, 781) for mild, moderate and severe renally impaired subjects, respectively, compared with healthy subjects. For C_{max} of naloxone-3-glucuronide, on average there was an increase to 148% (90% CI: 110, 197), 202% (90% CI: 151, 271) and 239% (90% CI: 179, 320) for mild, moderate and severe renally impaired subjects, respectively, compared with healthy subjects. For $t_{1/2}$ of naloxone-3-glucuronide, on average there was no significant change between the renally impaired subjects and the healthy subjects.

Overall, for oxycodone results for mild, moderate and severe renal impairment groups showed exposure to oxycodone was about 1.5, 1.7 and 2-fold higher than for the healthy subject group, respectively. The median T_{max} was 2.25 hours for the healthy subject group and this increased to 5 hours for subjects with mild renal impairment, whereas T_{max} values for the moderate and severe renally impaired groups were only slightly increased to 3.25 and 3.5 hours, respectively.

For the renal impairment group, the C_{max} of naloxone was roughly doubled for the mild and moderate renal impairment groups compared with the healthy subject group and about 3-fold increases were observed for the severe renally impaired group. The mean T_{max} also increased with the severity of renal impairment.

The results of study OXN1007 confirm that the pharmacokinetics of OXN10/5 mg PR were affected by renal impairment. In light of the results from study OXN1007 the sponsor suggests that a careful titration when starting and maintaining therapy with the fixed combination of oxycodone and naloxone should be considered for patients with compromised renal function.

Summary of Pharmacokinetics

The absolute bioavailability of naloxone following oral administration is negligible.

A significant level of systemic naloxone exposure is attained following intravenous or intra-nasal administration. The oxycodone PK profile from OXN PR has been shown to be bioequivalent to OxyPR. The pharmacokinetics of oxycodone and naloxone-3-glucuronide are dose-proportional.

Elderly subjects exhibited higher plasma concentrations of oxycodone; however this was not considered to be of clinical relevance because it is recommended that elderly subjects be dosed according to individual conditions and pain severity.

In renal impairment, the bioavailability of both oxycodone and naloxone was increased. It is therefore recommended that doses should be adjusted to the individual patient's condition and that patients should be observed for symptoms of overdose of either active substance. This is addressed in the proposed Product Information (PI) of OXN PR.

In moderate to severe hepatic impairment, the bioavailability of both oxycodone and naloxone was significantly increased. Consequently, moderate and severe hepatic impairment is a contraindication and is stated as such in the proposed PI. Caution should be exercised when administering OXN PR tablets for patients with mild hepatic impairment.

Pharmacodynamics

Pharmacodynamic data were presented from two studies that were performed in healthy subjects (study OXN1401) and in methadone stabilised opioid addicts (study OXN1402). Study OXN1402 was a dose escalation study with plasma concentration measurements in methadone-stabilised opioid addicts. Study OXN1401 was an exploratory study evaluating the influence of oxycodone and naloxone on electroencephalogram (EEG) parameters in an experimental pain model.

Study OXN1401 was a double-blind, placebo-controlled, 5-way crossover study in healthy subjects to assess to what extent naloxone PR tablets (5 mg, 15 mg and 45 mg) would antagonise the opioid agonist properties of oxycodone 20 mg, but pharmacokinetics were not well-characterised in the study. The duration of study and treatment included a 3-week screening period followed by 5 study periods each with a single dose of study drug followed by a 7-day washout period. The treatments were:

- 20 mg Oxycodone PR + 5 mg naloxone PR (1 x 5 mg + 2 placebo tablets)
- 20 mg Oxycodone PR + 15 mg naloxone PR (1 x 15 mg + 2 placebo tablets)
- 20 mg Oxycodone PR + 45 mg naloxone PR (3 x 15 mg tablets)
- 20 mg Oxycodone PR + 0 mg naloxone PR (3 placebo tablets)
- 0 mg Oxycodone PR + 0 mg naloxone PR (3 placebo tablets).

Results

Oxycodone results

In study OXN1401 similar amounts of oxycodone were available from each of the treatments. AUC_t values were not affected by increasing doses of naloxone. AUC_∞ values decreased slightly with increasing doses of naloxone and the bioavailability assessments showed that the open combination of oxycodone and naloxone (Oxy Nal) 20/5 mg provided an equivalent availability of oxycodone to oxycodone PR, whilst both Oxy Nal 20/15 mg and Oxy Nal 20/45 mg had bioavailability assessments that had 90% confidence intervals below the lower limit of acceptability for bioequivalence with respect to AUC.

The increasing doses of naloxone did not have an effect on the mean dose-adjusted C_{max} values for oxycodone. Relative to the OxyContin reference, mean oxycodone C_{max} ratios of 106.3%, 96.5% and 94.9% were associated with the 20/5 mg, 20/15 mg and 20/45 mg Oxy Nal combinations respectively. The associated 90% CI was within the 80-125% range in each case. The results supported the bioequivalence of oxycodone from all preparations with respect to C_{max}.

After administration of the open combination treatments and oxycodone PR tablet, the levels of noroxycodone were comparable to oxycodone (noroxycodone:oxycodone AUC_t and AUC_∞ ratios were between 0.75 and 1). Oxymorphone was present in much lower concentrations than oxycodone, consistent with what is known about oxycodone metabolism.

Naloxone-3-glucuronide results

Following oral administration plasma levels of naloxone were particularly low: after administration of Oxy Nal 20/5, only 6 subjects had measurable AUC_t values, meaning that any relative bioavailability calculations made using Oxy Nal 20/5 as the reference product would be of limited value. Therefore, PK and PD assessments were based on its primary metabolite naloxone-3-glucuronide (Table 1).

Taking into account the differences in naloxone dose, similar amounts of naloxone-3-glucuronide were available from each of the treatments. The bioavailability assessments showed that, in terms of AUC_t, Oxy Nal 20/15 was equivalent to Oxy Nal 20/5, with the 90% confidence intervals within 80-125%. The Oxy Nal 20/45 had a 90% confidence interval that was outside the upper limit of

acceptability for bioequivalence. The dose-adjusted C_{max} values for naloxone-3-glucuronide were consistent between the treatments.

Table 1: Study 1401- Summary of Pharmacokinetic Parameters for Naloxone-3-glucuronide by Treatment: Full Analysis Population for Pharmacokinetics

Pharmacokinetic parameter	**Oxy Nal 20/5**	**Oxy Nal 20/15**	**Oxy Nal 20/45**
AUC_t (ng.h/mL)			
Arithmetic mean (SD)	164.2 (42.73)	456.1 (150.15)	1592.9 (509.67)
C_{max} (ng/mL)			
Arithmetic mean (SD)	30.1 (12.30)	78.9 (22.03)	283.2 (129.24)
T_{max} (h)			
Median	1	1	1
(Min, Max)	(1,4)	(1,5)	(1,5)

Generally, the availability of oxycodone was similar from each of the active treatments. The oxycodone data suggest that the co-administration of naloxone PR tablets did not affect the pharmacokinetics of oxycodone. The availability of naloxone-3-glucuronide was variable; however the increase in naloxone-3-glucuronide availability was consistent with the increase in naloxone dosage.

Pharmacodynamic measures included pain-related evoked cerebral potentials (determined by EEG); phasic /tonic pain intensity estimates; EEG background activity; acoustic evoked potentials; tracking performance during phasic / tonic pain; sought symptoms (tiredness, nausea, dizziness and drowsiness).

Primary target parameters were pain-related evoked cerebral potentials:

1. Base-to-peak amplitudes P1, N1 and P2, peak-to-peak amplitudes P1N1 and N1P2 of pain related evoked potentials

2. Latencies P1, N1 and P2 of pain-related evoked potentials

3. Intensity estimates of phasic (CO2-) (a stream of carbon dioxide gas applied to a nostril) pain

4. Intensity estimates of tonic pain.

After painful stimulation of the nasal mucosa, subjects rated the intensity of the perceived pain by means of a visual analog scale (VAS). In study OXN1401 naloxone did not produce a significant reversal of oxycodone effects in amplitude P1 (Cz) after administration of a strong stimulus of 70% CO2. After administration of a weak stimulus of 60% CO2, naloxone produced a significant dose-dependent reversal of oxycodone effects in amplitude P1N1 (Cz).

The dose-dependent opioid antagonising effects of naloxone (reversal of reduction in amplitudes and prolongation of latencies) were shown to be more pronounced in response to weaker stimuli (60% CO2) than in response to stronger stimuli (70% CO2). A decrease in intensity estimates of phasic pain (VAS) stimuli with 70% CO2 was observed after administration of active treatments. A dose of 45 mg naloxone seemed to antagonise partly the oxycodone effect. However, compared to placebo, these effects were not statistically significant.

Results from the study suggested that there is a dose-dependent influence of naloxone on typical amplitude and latency changes, caused by oxycodone as an opioid. The data indicated that, based on

20 mg oxycodone PR, a dose of naloxone PR that does not significantly influence the analgesic effect (EEG) of oxycodone would be below 15 mg.

Study OXN1402 was a randomised, placebo-controlled, double-blind, oral dose escalation/dose finding and PK study to explore whether oral naloxone PR would improve bowel movement and/or induce symptoms of withdrawal in methadone stabilised opioid addicts.

The duration of study and treatment included two phases, a pre-phase and a main phase. Subjects were given 10 mg naloxone PR tablets in the pre-phase and 10, 20, 40, 70 and 100 mg naloxone PR (as multiples of 10 mg tablets) in the main phase of the study. In each period of the main phase there were 2 consecutive days, one with naloxone and one with corresponding placebo. Period 1: 10 mg on days 1 and 2; period 2: 20 mg on days 3 and 4; period 3: 40 mg on days 5 and 6; period 4: 70 mg on days 7 and 8; period 5: 100 mg on days 9 and 10. There was a washout period of at least 1 day between periods.

No PK parameters were calculated and no pharmacokinetic analysis was carried out because only a few measurements were available.

A primary endpoint of the main phase was bowel movement within 12 hours after study drug administration. Primary efficacy results are summarised in Table 2. Naloxone PR increased the frequency of bowel movements in a dose-dependent manner, and an effect could be seen starting from a naloxone dose of 20 mg. The full effect on the number of defaecations had already occurred on the second highest naloxone dose before doses inducing onset of withdrawal. There were no remarkable differences in the occurrence of defaecation between the second highest and the highest dose of naloxone, lending supportive evidence that the full effect of naloxone with regard to defecation already occurred on the second highest dose.

Table 2: Study 1402 - Primary Efficacy Results: Defaecation within 12 Hours of Dose -Full Analysis Population

	Second highest dose		**Highest Dose**	
	N	%	N	%
Defecations (yes/no), change from pre-dose				
-1	2	16.67	1	8.33
0	3	25.00	5	41.67
1	7	58.33	6	50.00

Naloxone PR reversed opioid-induced constipation but, in relation to constipation, the relationship between naloxone dose and opioid dose was unclear. Naloxone PR was also shown to induce withdrawal symptoms in these methadone-treated subjects, and for withdrawal there was a positive correlation between methadone dose and the naloxone dose at which withdrawal occurred (p-value: 0.020).

Importantly, naloxone PR began to reverse the opioid-induced constipation at doses well below those that caused the onset of withdrawal symptoms. Whilst the time course of this effect could not be fully investigated, it was noted that the onset of bowel movement and withdrawal usually occurred within the first 6 hours of naloxone PR administration.

In relation to withdrawal symptoms, pharmacodynamic parameters by treatment dose of naloxone were evaluated. Results suggested that, for skin colour and peristalsis quantity, there was no difference between naloxone or placebo at any dose. Pupil reactivity and peristalsis quality showed an increase under naloxone at certain doses, for example pupil reactivity at 70 mg naloxone and peristalsis quality at 70 mg and 100 mg naloxone. There was an increase in skin piloerection and

pupil size with naloxone compared to placebo, though the parameters were variable. Overall, from the parameters, the median dose of naloxone that induced clear symptoms of withdrawal appeared to be 70 mg.

Efficacy

The key Phase II/III studies providing pivotal data in the submission are:

- OXN2401 for demonstrating the influence of different combination ratios of oxycodone/naloxone on the primary endpoints of pain and bowel function
- OXN3001 for demonstrating improvement of opioid-induced constipation following OXN PR versus OxyPR tablets in doses up to 50 mg oxycodone PR
- OXN3006 for demonstrating improvement of opioid-induced constipation following OXN PR versus OxyPR tablet in doses up to 120 mg oxycodone PR, and
- OXN3401 for demonstrating superior analgesic efficacy following OXN PR versus placebo in doses up to 40 mg oxycodone PR per day in the Double-blind Phase and up to 80 mg in the Extension Phase.

The individual pivotal studies were not designed to demonstrate the non-inferiority of OXN PR to OxyPR in analgesic efficacy, therefore a meta-analysis (OXN9001) was planned in parallel to studies OXN3001 and OXN3006 and was specifically performed with this objective. The meta-analysis (OXN9001) combines the two randomised, double-blind, parallel group studies OXN3001 and OXN3006 aiming to demonstrate the non-inferiority of OXN PR to OxyPR in analgesic efficacy.

The objectives of the clinical Phase III studies were to confirm the results of the Phase I/II studies as well as to demonstrate the superiority of OXN PR regarding improvement in bowel function compared to subjects taking OxyPR, to demonstrate the superiority of OXN PR over placebo, and to confirm the comparability to OxyPR.

In studies OXN3001 and OXN3006 the primary objectives were to demonstrate the superiority of OXN PR over OxyPR with respect to bowel function as measured by the Bowel Function Index (BFI), while the primary objective in OXN3401 was to demonstrate the superiority of OXN PR over placebo with respect to analgesic efficacy. Long-term efficacy and safety of OXN PR up to a total daily dose of 80/40 mg was determined during the extension phase of the study OXN3401 (OXN3401S – Extension Phase) over a period of 12 months.

Standard assessments of constipation (for example, Bristol Stool Scale, frequency of bowel movements) can provide an objective assessment of the clinical status of a patient with constipation and response to treatment; however, these measures may not adequately reflect the impact of constipation experienced by the patient. The sponsor therefore developed and validated the Bowel Function Index (BFI) due to this lack of a gold standard for assessing opioid-induced constipation from a patient's perspective. The BFI was implemented in the Phase II and III development programme for OXN PR and was used as the primary endpoint in studies OXN3001 and OXN3006.

Further validation studies were initiated by the sponsor to demonstrate the psychometrics of the BFI items and to support the interpretation and use of these data. The validation programme was primarily based on data generated in the clinical Phase II study OXN2401 (A2-3759) and the Phase III studies OXN3001 (A2-4350) and OXN3401 (A2-4350). In addition, a cross-functional, non-interventional validation study A2-4351 in four European countries (Germany, UK, Italy and Czech Republic) was conducted to provide additional validation data.

In addition to the clinical programme, the sponsor submitted data from:

- a meta-analysis (OXN9001) combining the two randomised, double-blind, parallel group studies OXN3001 and OXN3006 to determine the safety and efficacy of OXN PR versus

OxyPR in subjects with moderate to severe chronic pain was performed. The primary objective of study OXN9001 was to demonstrate the non-inferiority of OXN PR to OxyPR in 12 week analgesic efficacy (subjects' Average Pain over the last 24 hours assessed at each double-blind study visit as measured by the Pain Intensity Scale)

- a post-marketing surveillance study (OXN9002). This prospective observational cohort study was performed as a multicentre study with outpatients suffering from pain over a planned duration of 4 weeks for each patient.

Study OXN2401 was a dose-finding study in patients with severe pain requiring opioid treatment who had a medical need for the regular intake of laxatives. This was a multicentre, prospective, controlled, randomised, double-blind (with placebo dummy), four group parallel study with oral OxyPR, oral naloxone (PR) and corresponding naloxone placebo. The study had three core phases: a pre-randomisation phase, a 4-week double-blind treatment period (maintenance phase) and a follow-up phase. The pre-randomisation phase consisted of screening and titration/run-in. Following screening, patients entered either a titration or run-in period. Patients with insufficient pain pre-treatment entered a minimum 2-week titration period and were individually titrated and stabilised at an oxycodone dose of 40 mg, 60 mg or 80 mg per day. Patients on stable oxycodone pre-treatment at screening (between 40-80 mg/day) and with concomitant constipation, entered a 1 week run-in period and were eligible for the maintenance phase without prior titration. For all patients, the dose of oxycodone could be adjusted during titration or run-in.

In total 202 patients were randomised and received double-blind medication. 196 patients completed the study, and 99 patients were assigned to the PP population. Patients enrolled were male or female aged ≥18 years who suffered from severe chronic pain of tumour and non-tumour origin and required opioid treatment.

Patients included in the double-blind treatment period were on stable oxycodone treatment and had a medical need for the regular intake of laxatives. Key exclusion criteria were:

- severe cardiovascular and respiratory disease
- severe liver and renal disease/dysfunction
- a history of paralytic ileus, psychoses, Parkinson's disease
- current pancreatitis
- patients who were pregnant or lactating, or female of childbearing potential and not adequately protected against conception.

At the end of the titration/run-in period, patients who were receiving a stable maintenance dose of 40 mg, 60 mg or 80 mg oxycodone per day (with no more than 5 rescue medication intakes per week) and had a medical need for the regular intake of laxatives were randomised to one of 3 naloxone treatment groups or a naloxone placebo treatment group. Each patient received a maintenance dose of oxycodone plus either 10 mg, 20 mg, 40 mg or naloxone placebo PR tablets daily. Self-medication of previously used laxatives by the patients was allowed. Patients were advised to stop laxative intake at the beginning of the maintenance phase (laxative intake was to be restarted if no bowel evacuations had occurred within 3 days after the start of double-blind treatment).

The laxative sodium picosulfate could be used as rescue medication as needed. No dose regimen was specified. Three stools should be passed at a minimum per week. If opioid typical side effects occurred, such as nausea or emesis, an antiemetic treatment could be given (no particular drug specified).

The protocol stated that all other concomitant medication was permitted, although the dosage/regime should remain constant during the subject's participation in the study.

After the treatment period, patients maintained their maintenance dose of oxycodone only for a further two-week follow-up phase (40 mg, 60 mg, or 80 mg oxycodone per day).

Results

Primary Efficacy Parameters

a) Mean Pain

Within the intention to treat (ITT) population during the 4-week treatment period (maintenance phase) there were no apparent differences in the intensity of mean pain observed. There were no relevant changes in mean pain intensity from randomisation to Visit 4 (with naloxone added to patients' treatment regimen) and the end of the maintenance phase for the absolute dose of naloxone groups or dose ratio groups.

Analysed by absolute naloxone dose (10 mg, 20 mg or 40 mg), mean pain intensity ranged from 38.3 (±18.49) to 38.8 (±16.59) compared to 36.9 (±15.74) for placebo during the last 7 days prior to Visit 4 and 37.2 (±17.24) to 38.7 (±17.05) compared to 37.8 (±18.22) for placebo during the last 7 days at the end of the maintenance phase. The differences between naloxone placebo treatment and the 10 mg, 20 mg and 40 mg naloxone treatments were small, and the 90% confidence intervals for the differences were narrow relative to the 0 to 100 pain scale. The results indicated that there was no negative effect of naloxone on the analgesic efficacy of oxycodone.

At randomisation mean (±SD) pain intensity ranged from 33.2 (±12.92) to 41.3 (±19.68) for the dose ratios. During the last 7 days of the maintenance phase mean (±SD) pain intensity ranged from 33.9 (±17.71) to 42.1 (±22.48) for all oxycodone/naloxone dose ratios and from 36.8 (±17.83) to 38.7 (±20.80) for all oxycodone/naloxone placebo dose ratios. Similar values were seen during the last 7 days prior to Visit 4 (first visit of treatment period) when mean (±SD) pain intensity ranged from 34.1 (±12.25) to 41.3 (±20.86) for the dose ratio groups.

Identical dose ratios were obtained for 40 mg oxycodone/10 mg naloxone and 80 mg oxycodone/20 mg naloxone (4:1) and for 40 mg oxycodone/20 mg naloxone and 80 mg oxycodone/40 mg naloxone (2:1). Within the 4:1 dose ratio group during the last 7 days at the end of the maintenance phase, mean pain intensity (±SD) of those patients taking 10 mg naloxone (40/10) was 33.5 (±22.13) and 49.1 (±20.88) for those taking 20 mg naloxone (80/20). In the 2:1 dose ratio group the values were 25.8 (±16.03) for those taking 20 mg naloxone (40/20) and 43.3 (±15.11) for those taking 40 mg naloxone (80/40). For both dose ratios, patients taking the higher naloxone and oxycodone dose recorded higher mean pain intensity scores at Visits 3, 4 and 5.

There was no major change in mean pain intensity from the end of the maintenance phase to the end of follow-up when patients were receiving oxycodone alone for the dose ratio groups or the treatment groups. The trends observed in the ITT population were also observed in the per protocol (PP) analysis for the intensity of mean pain.

b) Mean Bowel Function

Within the ITT population, a trend towards improved mean bowel function with increased dose of naloxone was seen. Analysis by absolute dose of naloxone showed values of 45.4 (±22.28), 40.3 (±23.09), 31.3 (±25.82) and 26.1 (±25.08) for placebo, 10 mg, 20 mg and 40 mg respectively at the end of maintenance ($p < 0.05$ for 20 mg and 40 mg naloxone versus placebo, t-test for difference) and 43.3 (±26.41), 42.1 (±25.53), 34.2 (±30.04) and 27.9 (±22.68) at Visit 4 ($p = 0.004$ for 40 mg naloxone versus placebo, t-test for difference).[1]

During the last 7 days at the end of the maintenance phase, mean (±SD) bowel function was lowest in the 1:1, 1.5:1 and 2:1 dose ratios (21.9±22.25, 21.8±21.35 and 26.7±23.98 for the 1:1, 1.5:1 and

[1] In this study, a development version of the BFI was used with a scale from 0-100.

2:1 dose ratios, respectively). Mean bowel function worsened as the amount of naloxone decreased, to a maximum value of 47.8 (±23.20) for a dose ratio of 6:1. For the last 7 days prior to Visit 4, mean bowel function ranged from 20.7 7 (±19.24) at a ratio of 1:1 to 45.7 (±26.86) at a ratio of 8:1. Values for mean bowel function in the oxycodone/naloxone placebo dose ratios were higher than in the 1:1, 1.5:1 and 2:1 dose ratios at both visits. Within both dose ratio groups 4:1 and 2:1 patients taking the higher oxycodone dose had higher mean bowel function values at Visits 3, 4 and 5.

From the end of the maintenance phase to end of follow-up, mean bowel function worsened. The range for mean bowel function was 21.8 (±21.35) to 48.2 (±21.71) for the dose ratio groups at end of maintenance and 33.2 (±20.76) to 52.1 (±26.79) for the dose ratio groups at the end of follow-up. The change was greatest in the 40 mg naloxone group; mean bowel function was 26.1 (±25.08) at the end of maintenance and 42.4 (±23.19) at the end of follow-up.

Analyses using the per protocol (PP) population were similar to those observed in the ITT population with regard to mean bowel function.

The data for the ITT population from study OXN2401 showed that the bowel function varies within an absolute naloxone dose for different oxycodone levels, and in particular, the patients with 20 mg or 40 mg naloxone dose showed markedly different bowel function values for different doses of oxycodone. However the data also support that the bowel function stays almost constant within the ratio of oxycodone/naloxone.

Additional post-hoc analyses confirmed the original statistical analysis, showing that the 2:1 and 1.5:1 dose ratios are significantly different versus the corresponding oxycodone dose plus naloxone placebo at both Visit 4 of the maintenance phase and Visit 5 at the end of maintenance. At Visit 5, all dose ratios, except the 8:1 ratio, achieved statistical significance versus the corresponding oxycodone dose plus naloxone placebo ($p<0.05$), however, only the 2:1 dose ratio showed statistical significance at the $p<0.001$ level. There was also a statistically significant difference in mean bowel function between the 2:1 and 4:1 dose ratios ($p=0.018$).

The additional post-hoc analysis also showed that bowel function decreases as the amount of naloxone decreases, within the same absolute oxycodone dose.

Estimates of treatment effect were calculated by combining the results from the different oxycodone/naloxone combinations, for example, the 2:1 ratio estimate was formed by averaging the predicted results of the 40/20 mg, 60/30 mg, and 80/40 mg oxycodone/naloxone combinations, relative to naloxone placebo. The estimated mean differences (SE) in mean bowel function for various oxycodone/naloxone ratios versus naloxone placebo groups are shown in Table 3. The results indicate that bowel function improvement increases as oxycodone/naloxone ratio decreases (as the naloxone component increases), with the estimated improvement at 2:1 approximately 50% higher than at 4:1 ($p<0.05$) and with a minimal improvement from the 2:1 ratio to the 1.5:1 ratio.

Table 3: Study OXN2401 - Response Surface Analysis of Bowel Function Efficacy by Oxycodone/naloxone Ratio (Estimated Improvement vs Naloxone Placebo)

Oxycodone/Naloxone Ratio	**Overall improvement (SE) versus Placebo**
6:1	8.0 (3.3)
4:1	11.0 (4.1)
3:1	13.4 (4.6)
2:1	16.2 (4.5)
1.5:1	16.5 (5.1)

Secondary Efficacy Parameters

1) Daily Pain Intensity

Daily pain intensity was stable for all treatment groups throughout the course of the maintenance phase. There were no clear trends or apparent differences seen in daily pain intensity between any absolute dose of naloxone treatment group. Daily pain intensity by dose ratio showed a similar trend.

2) Rescue Medication

No clear trend was observed in the numbers of patients taking rescue medication across all dose ratios. During the last 7 days at the end of the maintenance phase the mean (±SD) dose of rescue medication was highest in the 3:1, 4:1, 6:1 and 8:1 dose ratio groups (3.2±7.21, 2.6±5.20, 2.3±6.29, 4.1±10.54 respectively). During the last 7 days prior to Visit 4 the highest value of mean taken dose was 4.4 (±10.49) in the 80 mg oxycodone/placebo dose ratio. Throughout the entire maintenance phase, the highest value of 2.4 (±5.12) was in the 1.5:1 dose ratio group. No major differences were apparent in the 2:1 ratio group. In the 4:1 ratio there was a higher intake of rescue medication among those taking 20 mg naloxone (80/20) during the last 7 days prior to Visits 4 and 5: 4.3 (±6.54) compared to 0.5 (±0.92) in the 10 mg naloxone group (40/10) at the end of maintenance. The mean amounts (mg) of rescue medication during the last 7 days at the end of the maintenance phase were higher in the 10 mg and 20 mg naloxone groups.

3) Ease of Defaecation

For each active naloxone treatment group, improvements in ease of defaecation were seen during the last 7 days at the end of the maintenance phase ($p<0.05$ for all doses of naloxone versus placebo) and during the last 7 days prior to Visit 4 ($p<0.05$ for 20 mg and 40 mg naloxone versus placebo) as the dose of naloxone increased.

The mean values (±SD) at the end of the maintenance phase were 50.7 (±24.83), 44.8 (±24.85), 33.5 (±26.42) and 28.5 (±27.11) for placebo, 10 mg, 20 mg and 40 mg respectively. As expected from the results obtained for mean bowel function, the lowest mean values for ease of defaecation were recorded for dose ratios of 1:1, 1.5:1 and 2:1 at the end of maintenance (25.7±26.81, 24.3±23.69 and 27.6±24.86 respectively). The highest value at the end of maintenance (54.0±23.54) was recorded for the 80 mg oxycodone/placebo dose ratio.

Analysis by absolute dose of naloxone given the same oxycodone/naloxone dose ratio showed that within both dose ratio groups (4:1 and 2:1) patients taking the higher naloxone dose, and therefore also the higher oxycodone dose, had higher mean values for ease of defecation at Visits 4 and 5. However, those patients taking 40 mg oxycodone with 10 mg naloxone (4:1) or 20 mg naloxone (2:1) had lower mean values than the alternate dose of oxycodone (80 mg).

4) Feeling of Incomplete Bowel Evacuation

Improvements in feeling of incomplete bowel evacuation were seen during the last 7 days at the end of the maintenance phase and during the last 7 days prior to Visit 4 as the dose of naloxone increased. The mean (±SD) values at the end of the maintenance phase were 36.0 (±29.19), 33.5 (±26.37), 27.5 (±26.53), 23.6 (±25.11) for placebo, 10 mg, 20 mg and 40 mg naloxone ($p<0.05$ for 20 mg and 40 mg naloxone versus placebo).

5) Judgment of Constipation

Improvements in judgment of constipation were seen during the last 7 days at the end of the maintenance phase and during the last 7 days prior to Visit 4 as the dose of naloxone increased. The mean values (±SD) at the end of maintenance for placebo, 10 mg, 20 mg and 40 mg naloxone were 49.7 (±25.90), 42.6 (±28.51), 33.1 (±29.07) and 26.3 (±26.09).

6) Stool Frequency

For each treatment group there was a trend towards an increase in stool frequency with increasing dose of naloxone during the last 7 days prior to Visit 4, the mean (±SD) values being 0.9 (±0.46), 1.0 (±0.48), 1.2 (±0.82), 1.4 (±0.63) for placebo, 10 mg, 20 mg and 40 mg respectively ($p<0.001$ for 40 mg versus placebo). A similar but weaker trend was observed at the end of the maintenance phase with a statistically significant difference to placebo ($p<0.05$) recorded for 40 mg naloxone at the end of the maintenance phase.

7) Stool Consistency

The number of patients who had a median stool consistency of diarrhoea was highest in the 40 mg naloxone treatment group (3 (6.0%), 1 (2.1%), 3 (6.1%) and 9 (19.1%) for placebo, 10 mg, 20 mg and 40 mg naloxone respectively). No relevant differences were observed between each active treatment group.

8) Laxative Intake

The mean number of days with laxative intake during the last 7 days prior to the end of maintenance decreased with increasing absolute dose of naloxone (3.9±3.38, 2.6±3.34, 2.0±3.14, 1.6±2.93 for placebo, 10 mg, 20 mg and 40 mg naloxone respectively, $p<0.001$ for all doses of naloxone versus placebo). The percentage of days (mean ±SD) with laxation during the entire maintenance phase showed a clear decrease from placebo with increasing dose of naloxone. The values being 46.4±42.78, 36.5±39.50, 31.3±41.38 and 27.8±41.25 for placebo, 10 mg, 20 mg and 40 mg naloxone respectively. Overall, no clear trend regarding the mean laxative intake and the dose ratio could be identified.

9) Mean Laxative Dose

For each dose ratio, the number of patients qualifying for this analysis was small and varied at each study visit. No clear trends in percentage change in mean laxative dose could be observed for any dose ratio.

10) Global Assessment - Efficacy and Tolerability, Preference

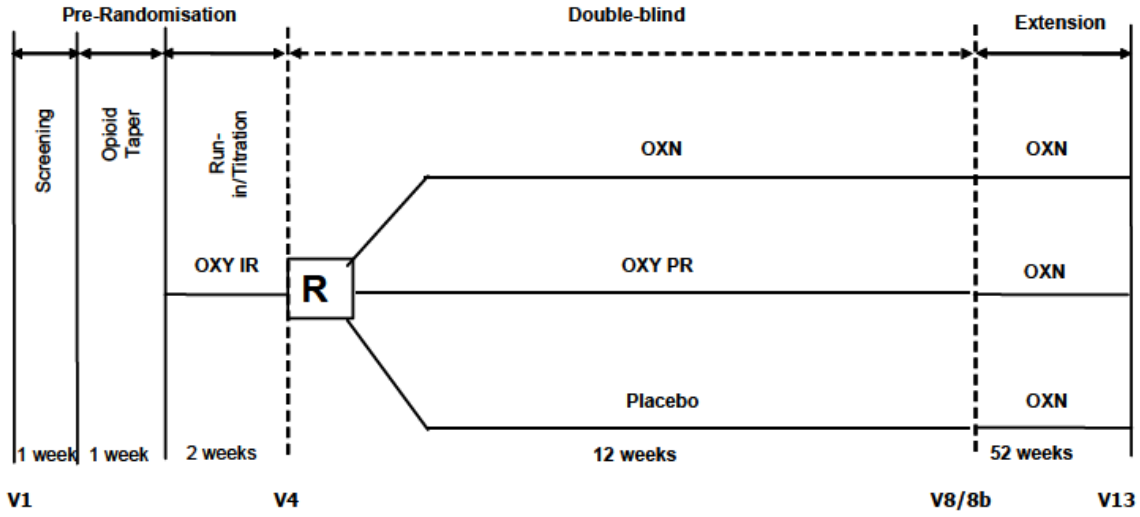
The 1:1 dose ratio was ranked good or very good by more patients and investigators than any other dose ratio. In total, 73.3% of investigators and 66.6% of patients rated the efficacy of the 1:1 dose ratio as good or very good. The 2:1 dose ratio was ranked good or very good by 59.4% of investigators and 59.4% of patients.

In relation to tolerability of medication, 86.7% of investigators and 80% of patients rated the tolerability of the 1:1 dose as good or very good. High ratings were also observed in the 80 mg/placebo dose ratio group (81.3% for investigators and 68.8% for patients), 8:1 dose ratio (77.3% for both investigators and patients) and 2:1 dose ratio (68.7% for investigators and 68.8% for patients). For efficacy, there was a trend towards better ratings with higher doses of naloxone.

Study OXN3401 was a randomised, double-blind, placebo- and active -controlled, double-dummy, parallel group study to determine the safety and efficacy of OXN PR in subjects with moderate to severe, chronic non-malignant pain (Low Back Pain, LBP).

The study design for study OXN3401 and OXN3401S is shown in Figure 11. The study consisted of three phases: a pre-randomisation phase (screening period, run-in period), a 12 week double-blind phase, and a 12 month extension phase (OXN3401S). The screening period involved prospective assessments and a pre-study opioid taper, and was designed to qualify subjects for participation in the run-in period. The run-in period was designed to titrate oxycodone immediate release (OxyIR) to analgesic effect, qualify subjects for participation in the double-blind phase, and enable identification of a starting dose equivalent to the study medication to be used after randomisation.

Figure 11: Study OXN3401 and OXN3401S - Study design



Subjects who achieved adequate analgesia with OxyIR were randomised to OXN PR, OxyPR or placebo. Subjects were converted from the effective dose of OxyIR to a fixed, symmetrical dose of the double-blind study medication (ie, OXN PR, OxyPR, or placebo) at a dose equivalent to 20 or 40 mg/d oxycodone.

The double-blind phase was designed to assess the safety and efficacy of OXN PR. Subjects who completed the double-blind phase could be enrolled into the extension phase to treat LBP with open-label OXN PR for up to 12 additional months. According to protocol a dose titration was permitted up to 80/40 mg/d OXN PR.

The Pre-randomisation Phase duration was up to 28 days and was designed to (a) assess inclusion/exclusion criteria, (b) confirm that opioids were required to treat the subject's moderate to severe LBP, (c) determine if the subject could achieve adequate analgesia with and tolerate OxyIR, and (d) identify the dose of study medication used during the Double-blind Phase.

Subjects eligible for the study must have had a documented history of moderate to severe chronic LBP that required around-the-clock opioid therapy and in addition LBP had to be adequately managed by an opioid for at least the past 2 weeks.

The duration of the Opioid Taper was up to 7 days. During this period the subject's opioid medication was down-titrated until the subject demonstrated the need for continued opioid treatment, and the eligibility for the Run-in Period was reviewed.

At randomisation visit (Visit 4), site study staff reviewed eligibility for randomisation and then randomised appropriate subjects into the Double-blind Phase. In the Double-blind Phase, subjects received double-blind study medication (ie, OXN PR, OXY, or placebo) for approximately 12 weeks and study visits occurred at weeks 2, 4, 8, and 12. Subjects were randomised in a 1:1:1 ratio to OXN PR, OxyPR, or placebo.

Laxatives were to be discontinued for 3 days after randomisation. After post-randomisation Day 3, use of a laxative(s) was permitted at the discretion of the investigator. Antidiarrhoeals could be used during the study.

One site enrolled 31 subjects of whom 24 were randomised. These subjects were excluded from all populations/analyses, after a recommendation of the committee who conducted an audit at this site with major adverse findings. The other sites enrolled 751 subjects into the study. 676 subjects entered the Opioid Taper. Of these, 73 subjects discontinued during the Opioid Taper.

The primary reason for discontinuation in the Opioid Taper was the experience of adverse events (AEs) (24 subjects, 3.6%). 139 subjects discontinued during the Run-in (Titration) Period, and the primary reason for discontinuation in the Run-in Period was lack of therapeutic effect. The mean age in the total population was 56.32 (SD ± 10.98) and was comparable across the three different treatment groups. The treatment groups were well balanced with respect to baseline characteristics. At the end of Run-in, pain values were generally low and stable. No major differences could be observed between treatment groups.

There were no relevant differences between treatment groups in terms of mean daily OxyIR doses at the end of the Run-in period. Mean daily OxyIR doses at the end of Run-in (end of up-titration) were around 27 mg, which fitted well in the dose range of the study (20 to 40 mgs).

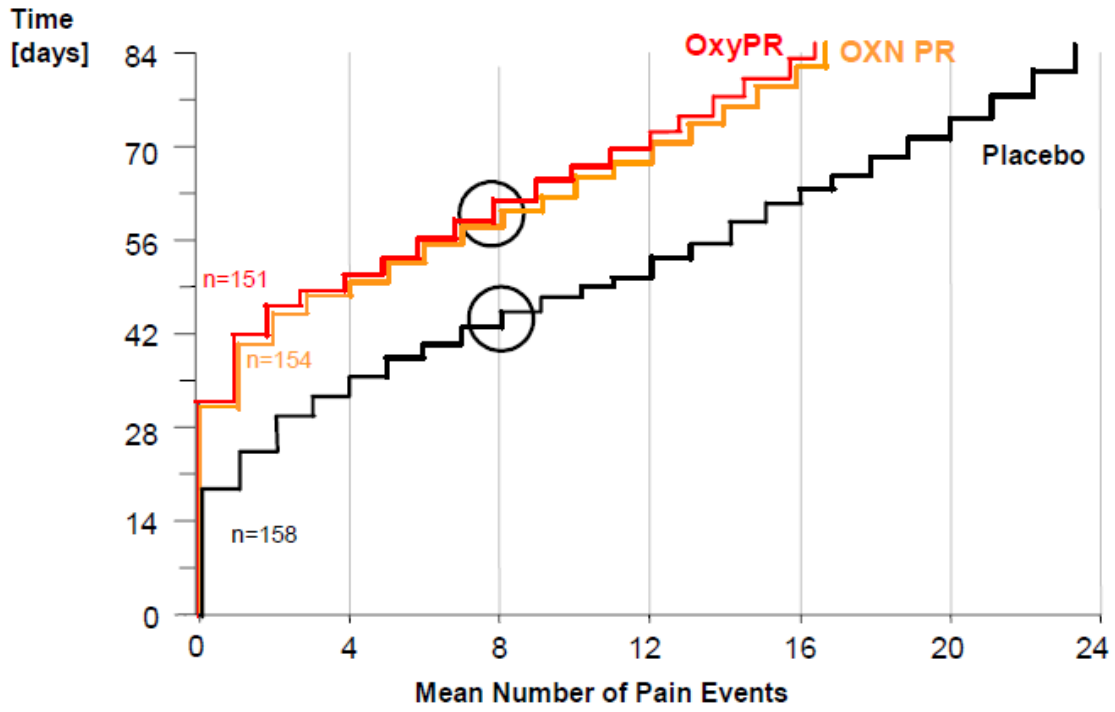
Similarly there were no major differences between treatment groups in terms of baseline bowel function. A subgroup analysis was performed, in which the subjects with a BFI ≥ 5 (using the Numeric Analysis Scale [NAS] 0 – 10) at Visit 4 were included.[2] The baseline BFI scores of these studies provide supportive evidence that BFI scores greater or equal to 5 are a good indicator that subjects are constipated.

Results

Primary efficacy parameters

The primary objective of the study was to demonstrate the superiority of OXN PR over placebo on the time from the initial dose of study medication to multiple (that is, recurring) pain events (inadequate analgesia) during the Double-blind Phase. Figure 12 presents the time to recurrent pain events over the mean number of pain events by treatment group in the full analysis population.

Figure 12: Study OXN3401 - Time to Recurrent Pain Events over Mean Number of Pain Events by Treatment Group: Full Analysis Population



[2] This study uses a development version of the BFI where a 0-10 scale was used. The final version employed a 0-100 scale.

Table 4 summarises the mean time to pain events for the per protocol population by treatment group. Pain events in the OXN PR group occurred 12 to 15 days later than in the placebo group. Pain events in the OxyPR group occurred 14 to 16 days later than in the placebo group. The times to pain event were significantly longer in the OXN PR group compared to the placebo group (p values between <0.0001 and 0.0003). There were no statistically significant differences between the OXN PR and the OxyPR group.

With the calculation of mean hazard ratios, it could be seen that for the Full Analysis Population, OXN PR was effective in reducing the risk of pain events, with an overall risk of 58% compared to placebo. This relative risk reduction was 42% which was statistically significant ($p < 0.0001$). The risk of experiencing a pain event was 6% higher with OXN PR treatment compared to treatment with OxyPR. This result was not statistically significant ($p = 0.6907$).

Table 4: Study OXN3401 - Mean Time (Days) to Pain Events: Per Protocol Population

Pain Event	Placebo (N = 94)	Oxycodone (N = 87)	Oxycodone / Naloxone (N = 82)	p-value OXN PR / Placebo	p-value OXN PR / Oxy
1	21.5	32.0	35.6	0.0039	0.5489
2	26.5	38.0	43.1	0.0012	0.4596
3	30.5	42.6	47.5	0.0023	0.5515
4	33.3	45.8	51.0	0.0028	0.4783
5	35.6	49.4	53.1	0.0011	0.6071
6	37.4	51.0	55.6	0.0007	0.4654
7	39.2	53.6	58.7	0.0006	0.6186
8	41.2	55.1	60.9	0.0003	0.4591
9	43.0	56.7	62.4	0.0002	0.3659
10	45.3	58.0	63.5	0.0004	0.3168
11	46.6	59.5	64.6	0.0004	0.3775
12	47.8	60.6	65.5	0.0004	0.3728

There were significant differences between the hazard ratios of each single pain event 1 to 12 in the OXN PR and placebo groups, and no such difference could be shown between the OxyPR and OXN PR groups. Within each treatment group, the hazard ratios of the single pain events were comparable.

For the per protocol population, results were similar. Overall, the results for the primary endpoint showed a significantly rarer appearance of pain events under OXN PR compared to placebo and a comparable incidence of pain events for OXN PR versus OxyPR.

Secondary efficacy variables

1) The "Average Pain over the Last 24 hours" Scores

In all treatment groups, the pain values slightly increased from baseline (Run-in pain) to Double-blind Phase, whereas during the Double-blind Phase pain values remained stable. Subjects in the OXN PR ($p = 0.0396$) as well as in the OxyPR ($p = 0.0080$) group showed statistically significant lower pain values compared to the placebo group throughout the Double-blind Phase. There was no statistically significant difference ($p = 0.5498$) between the pain values of the OXN PR and the OxyPR group.

2) The "Average Pain over the Last 24 hours" Scores (Subgroup Analysis (BFI ≥ 5 at V4)

In the subgroup analysis of BFI ≥ 5 , during the Double-blind Phase, pain values increased in the OxyPR group from 3.70 to 4.50 and in the placebo group from 3.59 to 4.58, whereas they stayed stable in the OXN PR group. In the last treatment period (days 57-84), pain values were around 10% lower under OXN PR treatment compared to OxyPR and placebo treatment.

3) Rescue medication used per day (24 hours)

Throughout the Double-blind Phase, the OxyIR intake in the placebo group was significantly higher compared to the OxyPR ($p<0.0001$) and OXN PR ($p=0.0004$) group. In the last treatment period (Days 57-84) the frequency of OxyIR intake in the placebo group was 51% higher compared to the OXN PR group.

Exploratory efficacy variables

The relevant comparison for all bowel function measurements was that between the OxyPR and OXN PR group.

1) Bowel Function Index (BFI): Full Analysis Population

Across the Double-blind Phase, subjects in the OXN PR group showed statistically significant lower (better) BFI scores compared to subjects in the OxyPR group ($p=0.0278$). In the subgroup of subjects with BFI values ≥ 5 at Visit 4, the decrease in the BFI scores showed a clinically relevant difference between the OXN PR group and the OxyPR group.[1]

2) Percentage of days with laxative intake during double-blind phase: Full Analysis Population and Subgroup Analysis (BFI ≥ 5 at V4)

Laxative use in the OXN PR group was lower than in the OxyPR group. Across the Double-blind Phase, subjects had a mean of 7.85% of days with laxative intake in the OXN PR group and 10.36% of days with laxative intake in the OxyPR group. During the study (from Days 1-28 to Days 57-84), laxative intake increased by 2.68 % with OxyPR and by 0.74% with OXN PR.

In the subgroup of subjects with BFI values ≥ 5 at Visit 4, laxative intake (mean % of days with laxative use) decreased over the course of the Double-blind Phase in the OXN PR group (18.36 to 15.63), and increased in the OxyPR group (13.71 to 24.26).

3) Complete Spontaneous Bowel Movements (CSBMs): Full Analysis Population and Subgroup Analysis (BFI ≥ 5 at V4)

Overall, the number of subjects who suffered from symptoms of constipation was low. In the OXN PR group, the mean number of CSBMs improved (increased) by 0.75 (from 4.83 to 5.58/week) whereas it remained stable in the OxyPR group. The percentage of CSBM1 responders (subjects who had at least one more CSBM in the week before the end of the Double-blind Phase compared to the week before baseline) was higher in the OXN PR group (46.10%) compared to the OxyPR group (29.14%). The percentage of CSBM3 responders (subjects who had at least three CSBMs in the week before the end of the Double-blind Phase) was higher in the OXN PR group (73.38%) compared to the OxyPR group (66.23%).

The population of subjects with BFI values ≥ 5 at Visit 4 was expected to be constipated, and this was reflected in the low CSBM values (between 1.89 and 2.40) that correlated with the high BFI values. In the subgroup of subjects with BFI values ≥ 5 at Visit 4, the mean number of CSBMs increased strongly (improved) by 2.27/week (1.93 to 4.20) with OXN PR and decreased (worsened) by 0.32/week (2.40 to 2.08) with OxyPR. The percentage of CSBM1 responders was higher in the OXN PR group (62.1%) compared to the OxyPR group (23.3%). The percentage of CSBM3 responders was higher in the OXN PR group (62.1%) compared to the OxyPR group (33.3%)

Study OXN3401S

Only subjects who completed the Double-blind Phase of study OXN3401 were eligible to enter the uncontrolled, open-label Extension Phase. In the Extension Phase, subjects were treated with open-label study medication (OXN PR) for up to 12 months. 380 subjects entered and 296 subjects completed the Extension Phase. All subjects entering the Extension Phase switched to a total daily dose of OXN20/10 mg PR to avoid subjects on placebo being switched to a high dose of opioid. Dose titration was permitted at the discretion of the investigator up to a maximum total daily dose of OXN80/40 mg.

The overall study objective was to assess the long-term efficacy and safety of OXN PR. The study was not powered for any primary efficacy variable. Secondary objectives of the study were: 1) to assess pain and interference of pain with activities during treatment with OXN PR based on the modified Brief Pain Inventory- Short Form (modified BPISF), and 2) to assess dose changes of OXN PR during the study period.

Results

BPI-SF Item

The BPI-SF item "average pain over the last 24 hours" was assessed on a 0 to 10 scale at every study visit with the last observation carried forward (LOCF). The mean pain scale value was 3.9 at Visit 9 (week 2), which was comparable to the mean pain scale value (3.8) at the end of the Double-blind Phase. Mean pain scale values remained low and stable over 6 months (mean Visit 11 = 3.7) and 12 months (mean Visit 13 = 3.8), indicating good analgesic efficacy during long-term treatment with OXN PR.

The sum scores of the 4 pain related BPI-SF items, which were assessed each on a 0 to 10 scale at every study visit were also analysed. After switching to the extension phase, the mean BPI-SF pain sub-score was 15.3 at Visit 9 (week 2), which is identical to the mean BPI-SF pain sub-score (15.3) at the end of the Double-blind Phase. Mean BPI-SF pain sub-scores remained low and stable over 6 months (mean Visit 11 = 14.6) and 12 months (mean Visit 13 = 14.8), once again supporting good analgesic effect during long-term treatment with OXN PR.

Dose changes during the extension phase

After the first two weeks of the Extension Phase, the majority of subjects remained on an OXN PR dose that was comparable to their treatment during the Double-blind Phase. The percentage of subjects with a dose increase or a dose decrease was similar and independent from the different treatment groups from which subjects were switched to OXN PR.

The majority of subjects remained on a stable OXN PR dose or had a slight dose decrease at the end of the Extension Phase. Up-titration was allowed as it was expected due to the natural progression of the underlying chronic pain condition over the 12-month study period. In the Extension Phase the mean total daily dose increased from 29.5 mg to 43.7 mg consistent with a natural progression of the underlying chronic pain condition.

Modified BPI-SF item "Sleep quality"

After switching to the Extension Phase, the mean sleep interference score was 2.9 at Visit 9 (week 2), compared to 3.1 at the end of the Double-blind Phase. Mean sleep interference scores were low and stable over 6 months (mean Visit 11 = 3.2) and 12 months (mean Visit 13 = 3.1), indicating a positive effect on sleep quality.

Subgroup analysis of subjects receiving doses above 40 mg/day OXN PR for more than 7 consecutive days

In a subgroup of subjects receiving higher doses than 40/20 mg OXN PR per day on more than 7 consecutive days, the mean average pain during the last 24 hours was stable and comparable at all visits throughout the Extension Phase, which supports that OXN PR is an effective analgesic drug in this subgroup population.

Study OXN3001 was a randomised, double-blind, double-dummy, parallel group, multicentre study in subjects with non-malignant pain taking OXN PR compared to subjects taking OxyPR alone. Subjects also had to have constipation secondary to opioid treatment.

The study consisted of three phases: a pre-randomisation phase (screening period, run-in period), a 12 week double-blind phase and a 12 month extension-phase. The screening period involved prospective assessments and was designed to qualify subjects for participation in the run-in period. The run-in period was designed to titrate OxyPR to analgesic effect, qualify subjects for participation in the double-blind phase, and enable identification of a starting dose equivalent for the study medication to be used after randomisation.

Subjects who achieved stable pain control in the run-in period and had confirmed opioid- related constipation were randomised to the double-blind study medication (i.e., OXN PR or OxyPR). Subjects were converted from the effective dose of OxyPR established during the run-in period (20-50 mg/d) to the equivalent dose (in mg of OxyPR per day) of the double-blind study medication. Open-label OxyIR was provided as pain rescue medication.

The 12 week Double-blind Phase was designed to assess the improvement in symptoms of constipation within 4 weeks as measured by the BFI and to compare pain efficacy within 12 weeks measured by the Numeric Analogue Scale (NAS) in subjects randomised to OXN PR compared to subjects randomised to OxyPR tablets alone.[3] Subjects who completed the Double-blind Phase had the option of entering the Extension Phase in which they received open-label OXN PR for up to 12 additional months. A dose titration in the Extension Phase was permitted up to 80/40 mg/day OXN PR. The Extension Phase was still ongoing at the time of the submission.

All laxative products, with the exception of oral Bisacodyl and fibre supplementations or bulking agents, were not allowed during the Pre-randomisation and Double-blind Phases. Subjects taking daily fibre supplementation or bulking agents were eligible for study participation if they could be maintained on a stable dose and regimen throughout the study, and in the investigator's opinion were willing and able to maintain adequate hydration. Antidiarrhoeals were permitted to be used during the study.

597 subjects were screened for entry into study OXN3001, 525 subjects were enrolled, 524 subjects were included in the safety run-in population and 322 subjects were randomised into the Double-blind Phase of the study. 160 subjects were randomised to receive OxyPR and 162 were randomised to receive OXN PR. 277 subjects completed the study. Adverse events (AEs) were the major reason for premature termination, and the rate was much higher in the OxyPR group (11.3%) than the OXN PR group (4.9%).

All subjects in the study suffered from moderate to severe, chronic non-malignant pain that required around-the-clock opioid therapy. There were no important demographic differences between the two treatment groups. The mean BFI (SD) at screening was 57.5 (23.10) in the OxyPR group and 58.1 (22.30) in the OXN PR group. BFI values at screening were comparable for both treatment groups at baseline. The mean PACOI (SD) at screening was 13.5 (6.82) in the OxyPR group and

[3] In this study, a scale of 0-100 was used for the BFI.

13.4 (6.80) in the OXN PR group.[4] Mean pain intensity (SD) at screening was 5.6 (2.00) in the OxyPR group and 5.6 (1.88) in the OXN PR. No differences between the treatment groups were apparent.

By the end of run in, the dosing level with the largest number of subjects was the 20 mg dose level. The number of subjects on 30 mg and 50 mg at the end of run-in was similar between groups. The overall mean daily double-blind doses of OxyPR and OXN PR were 33.0 mg (10.93) and 32.2 (11.26) mg respectively.

Results

Primary Efficacy Result

The primary objective of study OXN3001 was to demonstrate that subjects with moderate to severe non-malignant pain and who were taking OXN PR had an improvement in symptoms of constipation as measured by the BFI, compared to subjects taking OxyPR tablets. The main analysis was carried out with results from the 4 week time point of the double-blind phase (Visit6).

Table 5 summarises the primary efficacy results of OXN3001 by treatment group. Throughout the first 4 weeks of the Double-Blind Phase (Visit 3 to Visit 6) the difference between the mean BFI scores of the groups was statistically significant (OXN PR vs OxyPR, -15.2, p<0.0001; CI - 18.2, -12.2) and clinically relevant in favour of the OXN PR group (actually observed difference of the means was -16,7; OxyPR 51,6, OXN PR 34,9).

Table 5: Study OXN3001 - Primary Efficacy Results: Summary of the Bowel Function Index (BFI) by Visit (with LOCF) Full Analysis Population

Visit Name		Oxycodone PR	Oxycodone/Naloxone PR	Total
VISIT 3 (Randomisation)	N	158	158	316
	Mean (SD)	61.0 (23.39)	61.8 (22.95)	61.4 (23.14)
	Median	63.3	63.3	63.3
	Min, Max	0, 100	0, 100	0, 100
VISIT 4	N	158	158	316
	Mean (SD)	53.9 (26.32)	40.1 (26.26)	47.0 (27.15)
	Median	53.3	40.0	50.0
	Min, Max	0, 100	0, 100	0, 100
VISIT 5	N	158	158	316
	Mean (SD)	51.3 (27.93)	36.9 (26.90)	44.1 (28.31)
	Median	53.3	34.2	45.8
	Min, Max	0, 100	0, 100	0, 100
VISIT 6 (4 weeks)	N	158	158	316
	Mean (SD)	51.6 (26.78)	34.9 (25.80)	43.3 (27.56)
	Median	53.3	33.3	45.0
	Min, Max	0, 100	0, 100	0, 100
VISIT 7	N	158	158	316
	Mean (SD)	48.7 (27.04)	34.7 (27.25)	41.7 (28.00)
	Median	50.0	30.0	43.3
	Min, Max	0, 100	0, 100	0, 100
VISIT 8 (12 weeks)	N	158	158	316
	Mean (SD)	45.7 (29.88)	31.1 (26.76)	38.4 (29.25)
	Median	50.0	27.5	40.0
	Min, Max	0, 100	0, 90	0, 100
		OXN PR vs OXY: -15.2 p<.0001	CI:-18.2, -12.2	

[4] The Patient Assessment of Opioid-induced Constipation (PACOI) is a measure of the symptoms of constipation. It is 8 times the mean of the summary scores from the rectal and stool subscales of the PAC-SYM (the Subject Assessment of Constipation).

At Visit 3 bowel function was comparable between the two groups (mean (SD) of 61.0 (23.39) in the OxyPR group and 61.8 (22.95) in the Oxycodone/Naloxone PR group); however after four weeks (by Visit 6) mean BFI had improved in the Oxycodone/Naloxone PR group (34.9 (25.80)). The reduction of 26.9 points in the BFI score could be considered clinically relevant. In the OxyPR group there was a reduction in mean BFI score between Visit 3 (61.0 (23.39)) and Visit 6 (51.6 (26.78)), however the reduction of 9.4 points was not likely to be clinically relevant. This improvement in mean observed BFI score was seen early on in the Double-blind Phase (by Visit 4, 1 week after randomisation).

Reduction in mean BFI score continued beyond week 4 through to the end of the study (Visit 8) at which time there was still a statistical and clinically relevant difference in BFI score between the groups in favour of the OXN PR group (model estimated treatment difference OXN PR vs OxyPR, -14.6, $p<0.0001$; CI -20.7, -8.6).

Mean observed values at Visit 8 were 45.7 (29.88) in the OxyPR group vs 31.1 (26.76) in the OXN PR group. There was improvement in mean observed BFI scores within the OXN PR group, from a baseline of 61.8 (22.95) to the end of double-blind period value of 31.1 (26.76), which can be considered clinically relevant.

Results for BFI score without LOCF were similar to results with LOCF. The results for the primary analysis confirmed superiority of OXN PR over Oxy PR.

Symptoms of constipation - PACOI

PACOI was also analysed.[4] By the first 4 weeks of the Double-blind Phase the mean score in the OXN PR group (6.4 (5.29)) had reduced more than the mean score in the OxyPR group (9.4 (6.83)). The difference between the two groups was statistically significant (OXN PR vs OxyPR: -3.54; $p<0.0001$; CI, -4.56, -2.51) in favour of the OXN PR group. The difference between the groups was still apparent at Visit 8.

Pain Intensity Scale - Average pain over last 24 hours, as assessed at each visit

At baseline (Visit 3, the beginning of the Double-blind Phase) subjects had achieved stable pain control in the Run-in Period and had confirmed opioid-related constipation (less than 3 CSBM-NS in the last 7 days of the Run-in Period). The mean pain intensity scores were comparable between groups at Visit 3 and were maintained at this level through the Double-blind Phase to Visit 6, and on to the end of study (Visit 8). No statistically significant difference was noted between the two groups. Results were similar for the PP population with no treatment difference between OxyPR and OXN PR observed.

Exploratory Objectives

The number of complete spontaneous bowel movements (CSBMs) improved by 66% in the OXN PR group compared to the OxyPR group during the Double-blind Phase and the difference was statistically significant (OXN PR vs OxyPR, 1.66; $p<0.0001$; CI, 1.33, 2.07). The difference between the groups at 4 weeks into the Double-blind Phase was approximately 1 CSBM a week (mean (SD) 2.4 (2.56); median 2.0 with OxyPR vs mean 3.5 (2.81); median 3.0 with OXN PR). This improvement of one extra bowel movement a week with OXN PR could be considered clinically important in the case of chronic pain treatment.

By Visit 4 PAC-SYM and PAC-SYM(b) (Patient Assessment of Constipation) scores were reducing in both groups; however the reduction was greater in the OXN PR group (PAC-SYM: mean (SD);[4] 14.18 (9.04) in the OxyPR group and 10.60 (7.52) in the OXN PR group; PAC-SYM(b) mean (SD); 12.84 (10.10) in the OxyPR group and 9.48 (8.21) in the OXN PR group). After 4 weeks the scores in the OXN PR group were markedly lower than those of the OxyPR group (PAC-SYM: mean (SD); 12.69 (9.00) in the OxyPR group and 8.83 (7.17) in the OXN PR group; PAC-SYM(b) mean (SD); 11.59 (9.76) in the OxyPR group and 7.82 (7.72) in the OXN PR

group) and the difference between the groups was statistically significant for PAC-SYM (P=0.0001; CI -5.50, -2.83, by Visit 6). The results support that subjects receiving OXN PR had a statistically significant improvement in symptoms of constipation compared to subjects receiving OxyPR.

The Bristol Stool Scale is used to measure stool consistency, with type 1 being most hard (separate hard lumps, like nuts) and type 7 being most watery (watery, no solid pieces). Right from the start of the Double-blind Phase (Days 1-7), subjects in the OXN PR group had a higher percentage of days with at least one non-hard bowel movement compared to subjects in the OxyPR group (Mean (SD): 70.09 (23.53) vs 55.83 (29.12) respectively), and the trend continued to Visit 6 (Days 15-28, Mean (SD): 70.24 (25.40) vs 56.38 (27.04) respectively).

There was a strong statistically significant difference between groups with regard to laxative use during the first 4 weeks of the Double-blind Phase. Results for both the number of subjects who did not take laxatives (71 in the OxyPR group and 109 in the OXN PR group) and the number of subjects who did take laxatives (87 in the OxyPR group and 49 in the OXN PR) supported that subjects on OXN PR needed to take significantly fewer laxatives compared to those on OxyPR ($p<0.0001$).

BFI Validation Programme

The BFI is a 3-item questionnaire that was developed by the sponsor to measure constipation from the patient's perspective. The BFI is interviewer-administered and comprises three questions to assess constipation from the patient's perspective, rated on a numerical analogue scale (NAS) from 0 (good) to 100 (bad). The questions are:

1. Ease of defaecation (NAS) during the last 7 days according to patient assessment (0 = easy/no difficulty; 100 = severe difficulty).

2. Feeling of incomplete bowel evacuation (NAS) during the last 7 days according to patient assessment (0 = not at all; 100 = very strong).

3. Personal judgment of patient (NAS) regarding constipation during last 7 days (0 = not at all; 100 = very strong).

The items are averaged to get a summary score (total score range: 0 – 100). Additionally, each question is used on its own (item score range: 0 – 100).

Score changes below 9 are considered not clinically meaningful. Changes above 11 points are considered clinically meaningful for constipation, while scores between 9 and 11 are considered to require further evaluation.

As this questionnaire was a non-validated one it needed to be validated. The validation program consisted of the BFI validation with the data of the clinical Phase II OXN2401 (A2-4359), validation with the bowel data of the Phase III studies OXN3401 and OXN3001 (A2-4350 study code used for both clinical Phase III studies) and also of the cross-functional, non-interventional validation study A2-4351 in four European countries (Germany, UK, Italy and Czech Republic).

In the validation report A2-3759 the BFI was validated on the basis of the bowel parameters which were assessed in study OXN2401.

A further validation exercise (A2-4350) was performed, which consisted of the validation of the BFI based on the bowel parameters assessed in studies OXN3401 and OXN3001.

Study A2-4351 was a non-interventional study, in which the subjects had to come to the study site only once. Subjects eligible for the study must have had non-malignant pain and constipation caused/aggravated by opioids. During this study subjects were asked about their non-malignant pain condition, analgesic and laxative therapy and about their bowel parameters (stool frequency,

laxative intake). Subjects were asked about their BFI and to complete the PAC-SYM(b) questionnaire.

The items of the BFI related to one another as expected. Items 1 and 3 showed substantial overlap based on correlations. Content of item 2 did not overlap with items 1 and 3 as much as they overlapped with each other. The BFI items were internally consistent, suggesting they all measure similar related constructs. The BFI demonstrated reproducibility over time.

The relationships between BFI scores and patient reports regarding stool frequency and stool consistency were in the expected direction and all correlation coefficients met criteria for statistical significance. The number of days on laxatives related directly to BFI items. The BFI showed responsiveness to expected constipation changes over time, and the effect sizes increased in a dose-response fashion. The higher the naloxone dose, the higher the effect size for patients.

Validation of the BFI confirmed that changes in the BFI score of > 12 can be regarded as clinically relevant in symptoms of opioid induced constipation.

BFI validation on the basis of the studies OXN3401 and OXN3001

Validation of the Bowel Function Index (BFI): Secondary Analysis of OXN3401 Clinical Trial Data

A total of 460 participants at baseline were included in the final dataset. Participants completed the BFI at different assessment times.

There was very strong internal consistency found in the BFI suggesting the error level in the items is low and the items measure related constructs. Internal consistency as measured with Cronbach's alpha was very high for the BFI. The inter-item correlations among items and between items was strong. The BFI demonstrated reproducibility over time.

The relationships between BFI scores and related patient reports regarding stool frequency, stool consistency and completeness of bowel movement were in the expected direction. In addition all except one correlation met criteria for statistical significance (Item 2 and stool consistency; $r = 0.08$, ns). The BFI scores showed an expected and consistent pattern: patients with the fewest stools per week had the highest (worst) BFI scores.

Validation of the Bowel Function Index: Secondary Analysis of OXN 3001 Clinical Trial Data

323 participants at baseline comprised the evaluable population included in the final dataset. There were low response rates at floor values (best response indicating low constipation) at Visit 3 suggesting the BFI has the ability to detect improvement over time. The ceiling effects were also low indicating the BFI is a good measure of constipation severity. The BFI demonstrated strong internal consistency supporting that the error level in the items is low and they measure related concepts. Internal consistency as measured with Cronbach's alpha was high for the BFI, exceeding the 0.70 threshold considered necessary for group comparisons. The BFI demonstrated reproducibility over time.

The relationships between BFI scores and the PAC-SYM, PAC-SYM (b), and PACOI, were in the expected direction and all were in the moderate to large range. The relationships between BFI scores and patient reported clinical concepts such as stool frequency, stool consistency, and laxative use revealed small to moderate correlations between a patient assessment of constipation symptoms and the more traditional clinical assessments of constipation. The BFI and CSBM-NSND (no straining, no diarrhoea) and CSBM measures of frequency had stronger correlations than those between the BFI and SBMs suggesting CSBM-NSNDs and CSBMS may be better measures of stool frequency in this sample. Based on frequency of bowel movement, BFI scores were as expected: patients with the fewest stools per week had the highest (worst) BFI scores. The results showed that the BFI had good discriminant validity for severity of constipation as measured by stool consistency and by stool frequency.

Observational, Non-intervention, Multicentre Study for Validation of the Bowel Function Index for Constipation in European Countries

Study A2-4351 was a cross-sectional validation study to assess the psychometric properties of the BFI in a population of chronic non-malignant pain patients with opioid-induced constipation. The study was a multi-national study, which aimed to recruit approximately 120 patients across European countries (Germany, UK, Italy, Czech Republic). Eligible subjects had to visit the investigator on one occasion. Subjects completed four questionnaires and received no medication.

Results supported the construct validity of the BFI total and item scores; there were moderate to strong correlations observed with objective clinical-based measures such as stool frequency and stool consistency. Based on the previous analyses of the BFI, correlations in this study were slightly higher for these clinical-based measures but the correlations between the BFI and days on laxative did not show the expected relationship. The magnitude of the correlations between stool frequency and consistency and patient-reported constipation indicated that the clinical measures and patient-reported outcomes provide complementary, but not identical, information on constipation-related outcomes.

There was moderate to strong significant correlation between other patient-reported constipation measures (PAC-SYM and PAC-SYM (b)) and BFI scores. The PAC-SYM can be considered a valid and reliable measure of patient-reported constipation symptoms. In this study there was good evidence supporting the internal consistency reliability of the BFI with a Cronbach's alpha of 0.86.

Overall the study results supported the internal consistency reliability and validity of the BFI in chronic pain patients with constipation. The BFI was shown to be a reliable and valid measure of constipation-related symptomatology in chronic pain patients that can provide additional information on constipation-related outcomes that complements clinical outcomes reported in clinical trials.

Study OXN3006 was a randomised, double-blind, double-dummy, parallel group, multicentre study in subjects with non-malignant pain taking OXN PR compared to subjects taking OxyPR alone. Subjects had to have constipation secondary to opioid treatment.

The study consisted of three phases: a pre-randomisation phase (screening period, run-in period), a 12 week double-blind phase and a 12 month extension-phase. The screening period was designed to qualify subjects for participation in the run-in period. The run-in period was designed to titrate OxyPR to analgesic effect, qualify subjects for participation in the double-blind phase, and enable identification of a starting dose equivalent for the study medication to be used after randomisation.

Subjects who achieved stable pain control in the run-in period and had confirmed opioid- related constipation were randomised to the double-blind study medication (that is, OXN PR or OxyPR). Subjects were converted from the effective dose of OxyPR established during the run-in period (60-80 mg/d) to the equivalent dose (in mg of OxyPR per day) of the double-blind study medication in a stepwise manner during the first 4 days of the double-blind phase. Open-label OxyIR was provided as pain rescue medication, and Bisacodyl was used, if required.

The 12 week double-blind phase was designed to assess the improvement in symptoms of constipation within 4 weeks as measured by the BFI and to compare pain efficacy within 12 weeks measured by the NAS in subjects randomised to OXN PR compared to subjects randomised to OxyPR tablets alone.

Subjects who completed the double-blind phase had the option of entering the extension phase in which they received open-label OXN PR for up to 12 additional months. A dose titration in the extension phase is permitted up to 120/60 mg/day OXN PR. The extension phase was still ongoing at the time of the submission.

All laxative products, with the exception of oral Bisacodyl and fibre supplementations or bulking agents, were not allowed to be used during the Pre-randomisation and Double-blind Phases. Subjects taking daily fibre supplementation or bulking agents were eligible for study participation if they could be maintained on a stable dose and regimen throughout the study, and in the investigator's opinion were willing and able to maintain adequate hydration. Antidiarrhoeals could be used during the study.

379 subjects were screened for entry into the study, 347 subjects were enrolled, 331 subjects were entered in the safety run-in period and 278 subjects were randomised into the double-blind phase of the study. 135 subjects were randomised to receive OxyPR and 130 were randomised to receive OXN PR. 13 subjects were excluded because of study questionnaire irregularities. 222 subjects completed the study, and the discontinuation rate was low and similar in both treatment groups (15.6 % in the OxyPR group, 16.9 % in the OXN PR group). The main reason for early discontinuation was subject's choice.

All subjects in the study suffered from moderate to severe chronic non-malignant pain that required around-the-clock opioid therapy and had constipation caused or aggravated by an opioid treatment. The treatment groups were similar with respect to baseline demographic characteristics.

The primary objective of study OXN3006 was to demonstrate an improvement in bowel function in subjects treated with OXN PR compared to subjects receiving oxycodone PR, with bowel function being assessed based on the BFI and PAC-SYM values. The mean BFI (SD) was comparable for both treatment groups: at screening 65.6 (19.64) in the OxyPR group and 67.4 (19.24) in the OXN PR group. Baseline characteristics with respect to mean pain intensity were also in the two treatment groups. The mean average daily dose was comparable between both treatment groups: overall mean daily double-blind doses of OxyPR and OXN PR were 71.9 mg (14.81) and 74.4 (13.57) mg respectively.

Results

Primary Efficacy Results

The comparison of mean BFI scores after 4 weeks of the Double-blind Phase was the primary analysis for the primary objective of this study. Results showed that throughout the first 4 weeks of the Double-blind Phase (Visit 3 to Visit 6) the difference between the mean BFI scores of the groups was statistically significant (OXN PR vs OxyPR, -14.9, $p<0.0001$; CI - 17.9, -11.9) and clinically relevant in favour of the OXN PR group (actual observed difference of the means was –12.3; OxyPR 53.27, OXN PR 40.94). At visit 3 bowel function was comparable between the 2 groups; however after four weeks (by Visit 6) mean BFI had improved considerably in the OXN PR group (40.94 (27.38)). The reduction of 26.46 points in the BFI score is likely to be clinically relevant.

In the OxyPR group there was a reduction in mean BFI score between Visit 3 (64.09 (19.84)) and Visit 6 (53.27 (23.86)); however this reduction of 10.77 points was unlikely to be clinically relevant (change in the BFI score > 12 is defined as a clinical relevant difference). Improvement in mean observed BFI score was seen early on in the Double-blind Phase (by Visit 4, 1 week after randomisation, the mean BFI score in the OXN PR group had already reduced by 23.24 points to 44.16 (26.53). The reduction in mean BFI score (SD) continued past the 4 week stage to the end of the study (Visit 8) at which time there was still a clinically relevant difference in BFI score between the groups in favour of the OXN PR group. These results confirmed the superiority of OXN PR over OxyPR based on primary analysis.

Symptoms of constipation – PACOI

The decrease of the mean (SD) PACOI from baseline (V3) to V6 was more pronounced in the OXN PR group compared to the OxyPR treatment group. At V6 the mean (SD) PACOI describing

"bothersomeness" was 1.07 (0.78) in the OxyPR treatment group, whereas the value in the OXN PR treatment group was 0.75 (0.70). Corresponding PACOI – "symptoms" values were 1.12 (0,75 and 0.79 (0.65)) in the OxyPR group and OXN PR group respectively. The difference between the two groups was statistically significant in favour of the OXN PR group for both PACOI sub-scores (Bothersomeness and Symptoms) (PACOI Bothersomeness: OXN PR vs OxyPR: -1.93; p<0.0001; CI, -2.34, -1.52; PACOI-Symptoms: OXN PR vs OxyPR: -1.89; p<0.0001; CI, -2.27, -1.51). Once again this reduction in score was already apparent in the OXN PR group by Visit 4, and the difference between the groups was still present at Visit 8.

Pain Intensity Scale - Average pain over last 24 hours, as assessed at each visit

The mean pain intensity scores were comparable between groups at Visit 3 and remained at this level through the Double-blind Phase to Visit 6, and on to the end of study (Visit 8). There was no statistically significant difference between the two groups.

Exploratory Objectives

As expected, the number of CSBMs per week improved by 117% in the OXN PR group compared to the OxyPR group during the Double-blind Phase and the difference was statistically significant. At the end of the first 4 weeks of the Double-blind Phase subjects treated with OxyPR had only approximately 46% of the number of CSBMs of subjects receiving OXN PR (OXN PR vs OxyPR: 0.46; p<0.0001; CI, 0.37, 0.58). The difference between the groups at 4 weeks into the Double-blind Phase (Visit 6) was approximately 1.25 CSBM a week (mean (SD) 1.8 (2.01); median 1.0 with OxyPR versus mean of 3.07 (2.88); median 3.0 with OXN PR).

Within the first week of the Double-blind Phase (Days 1-7) subjects in the OXN PR group had a higher percentage of days with at least one non-hard bowel movement compared to subjects in the OxyPR group (Mean (SD): 70.23 (24.12) vs 50.41 (25.35) respectively). The trend continued to Visit 6 (Days15-28, Mean (SD): 67.76 (24.31) vs 54.36 (23.66) respectively).

There was a statistically significant difference between groups in relation to laxative use during the first 4 weeks of the Double-blind Phase. Results for both the number of subjects who did not take laxatives (49 in the OxyPR group and 74 in the OXN PR group) and the number of subjects who did take laxatives (86 in the OxyPR group and 56 in the OXN PR group) indicated that OXN PR-treated subjects needed to take significantly fewer laxatives compared to those on OxyPR (p<0.0001).

In terms of daily mean pain intensity scores, results were comparable between the two treatments. There were no statistical differences between treatment groups (OXN PR – OxyPR 0.10, CI: -0.14, 0.34, p- value 0.406).

Mean supplemental analgesic use was low and comparable in both treatment groups at baseline and throughout the Double-blind Phase up to the end of study. Between Days 1 – 28 the mean (SD) daily supplemental analgesic use was 0.9 (0.7) intakes in the OxyPR treatment group and 1.1 (0.7) in the OXN PR treatment group. During Days 57 – 84 of the Double-blind Phase the mean (SD) supplemental analgesic use was 0.8(0.7) in the OxyPR group and 0.9 (0.7) in the OXN PR group. Results showed there was no statistically significant difference between the groups with respect to the frequency of rescue medication intake.

Subgroup Analysis

After unblinding of the database a post-hoc subgroup analysis of subjects receiving more than 80 mg/day oxycodone PR on more than 7 consecutive days was conducted.

At Visit 3 bowel function was comparable between the 2 groups (mean (SD) of 61.88 (21.32) in the Oxy PR group and 68.21 (21.25) in the OXN PR group); however after 4 weeks mean BFI had improved considerably in the OXN PR group (37.63 (29.87)), a reduction of 30.58 points in the BFI

score that was clinically relevant. In the OxyPR group there was a reduction in mean BFI score between Visit 3 (61.88 (21.32)) and Visit 6 (55.09 (24.14)) but this reduction was only 6.79 points. Once again the improvement in mean observed BFI score was seen early on in the Double-blind Phase. The reduction in mean BFI score continued past the 4-week stage to the end of the study (Visit 8) at which time there was a difference in BFI score between the groups in favour of the OXN PR group: at Visit 8 scores were 49.65 (30.01) in the OxyPR group compared to 39.23 (30.87) in the OXN PR group. No statistical analysis was performed for this subgroup due to the small number of patients; however results were consistent with those for the overall population and indicated superiority of OXN PR over OxyPR based on primary analysis of the BFI.

As expected, the number of CSBMs per week improved in the OXN PR group compared to the OxyPR group during the Double-blind Phase. The mean (SD) number of CSBMs in the last 7days prior to Visit 6 were 1.71 (1.38) in the OxyPR group and 3.44 (3.39) in the OXN PR group. The difference between the groups at 4 weeks into the Double-blind Phase (Visit 6) was approximately 2.0 CSBM a week (mean (SD) 1.7 (1.38); median 1.0 with OxyPR vs mean 3.44 (3.39); median 2.0 with OXN PR). These differences can be considered clinically relevant.

Study OXN 9001 - Meta-analysis

In addition to the clinical programme, the sponsor submitted a meta-analysis (OXN9001) combining the two randomised, double-blind, parallel group studies OXN3001 and OXN3006 to determine the safety and efficacy of OXN PR versus OxyPR in subjects with moderate to severe chronic pain. The primary objective of study OXN9001 was to demonstrate the non-inferiority of OXN PR to OxyPR in 12 week analgesic efficacy (subjects' Average Pain over the last 24 hours assessed at each double-blind study visit as measured by the Pain Intensity Scale).

Secondary objectives of this study were: 1) to determine the frequency of rescue medication used per day (24 hours) by subjects receiving OXN PR and OxyPR, 2) to determine the symptoms of constipation during treatment with OXN PR compared with OxyPR based on the laxative intake and BFI, and 3) to compare the safety profiles of OXN PR and OxyPR.

587 subjects were included in the double-blind safety (DB safety) population which was employed for the safety analysis and 581 subjects were included in the full analysis population which was employed for the efficacy analysis. 429 subjects were included in the per protocol population.

Results

Primary Efficacy Results

Throughout the 12 weeks of the Double-blind Phase (Visit 3 to Visit 8) results for mean pain intensity by visit and treatment group were similar in both treatment groups and there was no statistically significant difference between the two groups. Non-inferiority (non-inf) of OXN PR to OxyPR was demonstrated for the per protocol population (OXN PR vs OxyPR, 0.08; non-inf $p<0.0001$; CI -0.07, 0.23). In addition, for the Full Analysis Population no treatment difference between OXN PR and OxyPR could be observed (OXN PR vs OxyPR, - 0.01; non-inf: $p<0.0001$; CI -0.15, 0.13). The LOCF results also showed non-inferiority of OXN PR to OxyPR (OXN PR vs OxyPR, -0.01; non-inf: $p<0.0001$; CI -0.14, 0.13). These results confirmed the non-inferiority of OXN PR over OxyPR based on primary analysis of the Average Pain over the last 24 hours.

Analgesic Rescue Medication Intake

Between Days 1 – 28 of the Double-blind Phase the mean (SD) daily supplemental analgesic use was 0.7 (0.70) uses in the OxyPR treatment group and 0.8 (0.72) in the OXN PR treatment group. During Days 57 – 84 the mean (SD) supplemental analgesic use was 0.7 (0.70) in the OxyPR group and 0.7 (0.69) in the OXN PR group. There was no statistically significant difference between the groups. Results were similar for the Full Analysis Population.

BFI Scores

At Visit 3 (baseline) bowel function was comparable between both treatment groups (mean (SD) of 62.4 (21.84) in the OxyPR group and 64.3 (21.61) in the OXN PR group). Throughout the 12 weeks of the Double-blind Phase (Visit 3 to Visit 8) the difference between the mean BFI scores of the groups of the Full Analysis Population with LOCF was statistically significant (OXN PR vs OxyPR, -15.1, p<0.0001; CI -17.3, -13.0) and clinically relevant in favour of the OXN PR group (actual observed difference of the means was –14.7; OxyPR 47.1, OXN PR 32.4). The non-LOCF results also showed statistically significant results in favour of OXN PR to OxyPR (OXN PR vs OxyPR, -15.3, p<0.0001; CI -17.5, -13.1). Significant treatment differences between OXN PR and OxyPR were also observed for the Per Protocol population (OXN PR vs OxyPR, -15.1, p<0.0001; CI -17.6, -12.6). The results confirmed the superiority of OXN PR over OxyPR based on BFI scores.

Study OXN9002 was a post-marketing surveillance study. It was a prospective observational cohort study that was performed as a multicentre study over a planned duration of 4 weeks for each patient, in outpatients suffering from pain. The maximum total daily dose of OXN PR was OXN20/10 mg PR twice daily. In a global assessment, efficacy and tolerability of OXN PR (marketed product Targin) and possible reasons for early discontinuation were assessed.

Standardised pain questionnaires (for example, BPI-SF) were enclosed to the patient documentation form (PDF) and to be filled out together by the physicians and patients at each of the 4 visits. Pain intensity (strongest/ slightest/ mean/ current pain) and impairment of different areas of life (general activity, mood, ability to walk, strength, relationship, sleep, vitality) were assessed by means of a numerical rating scale ranging from 0 = no pain/ impairment to 10 = strongest pain/ impairment. Bowel function was assessed using the Bowel Function Index (BFI).

In total 4578 patients filled out at least 1 pain questionnaire which could be evaluated. All subjects entering this observational study suffered from pain which required an opioid analgesic therapy. Pain-causing underlying disease(s) were requested for the musculoskeletal system, nervous system, and tumour.

The mean age (SD) in the total population was 65.8 (13.6) and the mean age of the two subgroups was also comparable. Approx. 2/3 of the whole population was female and 1/3 was male.

At the Initiation visit subjects were switched from their analgesic pre-treatment to OXN PR and the dose of OXN PR, which the subjects received in the morning and in the evening was assessed at every visit. The maximum anticipated dose of OXN PR was OXN20/10 mg PR twice daily.

Results

Analysis of analgesic efficacy

The rating of strongest pain (SD) decreased from 6.8 (1.8) at the initiation visit to 3.9 (2.1) at the 3rd control visit in the total population. For opioid- naïve subjects mean value of strongest pain at the initiation visit was 7.0 (1.7), which decreased to 3.6 (2.0) at the 3rd control visit. In opioid-pre-treated subjects the mean value of strongest pain was 6.7 (1.8) at the initiation visit and 4.0 (2.1) at the 3rd control visit.

Mean pain intensity (SD) during the last 24 hours decreased from 5.6 (1.8) at the initiation visit to 3.2 (1.8) at the 3rd control visit. In opioid-naïve subjects mean pain intensity decreased from 5.9 (1.7) to 3.0 (1.8) at the 3rd control visit. Mean pain intensity in opioid-pre-treated subjects was 5.5 (1.8) at the initiation visit and 3.3 (1.8) at the 3rd control visit.

Analysis of the effect of OXN PR on the bowel function

The mean BFI value (SD) in the total population decreased from 38.2 (30.9) at the Initiation visit to 15.1 (18.6) at the 3rd control visit. In opioid-naïve patients the mean of BFI decreased from 23.3

(27.2) at the initiation visit to 12.0 (16.8) at the 3rd control visit. For opioid-pre-treated patients the BFI decreased from 43.2 (30.5) at the initiation visit to 16.2 (19.0) at the 3rd control visit.

Overall results showed that treatment with OXN PR lead to a clinically significant reduction in pain values. Results with regard to effect of OXN PR on the bowel function demonstrate a clinically significant reduction in BFI values.

Summary of Efficacy

The clinical trial programme demonstrated that OXN PR and OxyPR showed similar analgesic efficacy (studies OXN3401, OXN3001 and OXN3006) up to a total daily dose of OXN120/60 PR mg. Results of the meta-analysis (OXN9001) were also consistent with this. In addition it was demonstrated in studies OXN3001 and OXN3006 that subjects receiving OXN PR had an improvement in bowel function compared to subjects receiving OxyPR alone. The laxative intake was significantly decreased. Improvement in bowel function was demonstrated in a subgroup of constipated subjects (BFI ≥ 50) in study OXN3401 receiving OXN PR compared to OxyPR.

In the clinical programme there were a limited number of patients who received a dose of OXN120/60 PR mg daily. The pivotal efficacy findings in the Phase III studies are supported by the dose finding study OXN2401 and the post- marketing surveillance study OXN9002. In study OXN2401 it was shown that OXN PR and OxyPR provide similar analgesic efficacy. It was also demonstrated that subjects receiving the combination of oxycodone and naloxone in a ratio of 2:1 up to a total daily dose of 80/40 mg was associated with an improvement in bowel function compared to subjects receiving OxyPR alone. After termination of the double-blind phase subjects were switched to a treatment with OxyPR alone within a follow-up phase of 2 weeks, and during this period the BFI value of the subjects increased again. This observation indicates that the naloxone component of OXN PR can be used for the treatment and prophylaxis of opioid-induced constipation.

The observational study, OXN9002, demonstrated that OXN PR is an effective analgesic and resulted in an improvement in bowel function.

The evaluator considered that the efficacy data presented for evaluation have adequately demonstrated that OXN PR is an effective opioid analgesic up to a total daily dose of OXN120/60 mg PR. Furthermore it has been shown that the naloxone component in fixed combination with oxycodone is effective for the therapy and/or prophylaxis of opioid-induced constipation.

In the clinical programme a limited number of patients received a dose of OXN120/60 PR mg daily, and therefore it is appropriate that a maximum total daily dose of 80 mg of oxycodone and 40 mg of naloxone (OXN80/40 mg PR) should be recommended for treatment of pain.

Safety

Study OXN3001

Extent of Exposure

The overall mean daily doses of OxyPR and OXN PR were 33.0 mg (10.93) and 32.2 (11.26) mg, respectively. The majority of subjects received study medication for 12 weeks (≥ 85 days). 87% of subjects in the OXN PR group and 82.5% of subjects in the OxyPR group received study medication for ≥78 days (approximately ≥11 weeks). Mean duration of exposure was similar in both treatment groups (76.8 days in the OxyPR group and 77.8 days in the OXN PR group). Most of the subjects continued on the same dose of study medication from time of randomisation to the end of the Double-blind Phase.

Adverse Events (AEs)

Common Adverse Events

Table 6 provides an overview of AEs in the Double-blind Phase, while Table 7 presents common AEs; those with a System Organ Class (SOC) incidence of ≥10% and Preferred Term incidence of ≥1% in any treatment group, by MedDRA term.

Table 6: Study OXN3001 – Overview of Adverse Events: Double-blind Safety Population

	OxyPR (N=160)	%	OXN PR (N=162)	%	Total (N=322)	%
Number of AEs	305	.	292	.	597	.
Number of subjects with AEs	102	63.8	98	60.5	200	62.1
Number of related AEs	149	.	148	.	297	.
Number of subjects with related AEs	60	37.5	57	35.2	117	36.3
Number of Severe AEs	39	.	32	.	71	.
Number of subjects with severe AEs	21	13.1	14	8.6	35	10.9
Number of SAEs	12	.	4	.	16	.
Number of subjects with SAEs	9	5.6	3	1.9	12	3.7
Number of related SAEs*	5	.	2	.	7	.
Number of subjects with related SAEs*	4	2.5	1	0.6	5	1.6

* Assessed by the investigator

Table 7: Study OXN3001 - Incidence of Adverse Events by System Organ Class (≥10%) and Preferred Term (≥1%): Double-Blind Safety Population

SOC (a) MedDRA Preferred Term	OxyPR (N=160)	%	OXN PR (N=162)	%	Total (N=322)	%
GASTROINTESTINAL DISORDERS	48	29.6	31	19.4	79	24.5
Dyspepsia	4	2.5	1	0.6	5	1.6
Diarrhoea	11	6.8	9	5.6	20	6.2
Constipation	8	4.9	1	0.6	9	2.8
Abdominal Pain	7	4.3	2	1.3	9	2.8
Abdominal Pain Upper	2	1.2	2	1.3	4	1.2
Nausea	17	10.5	10	6.3	27	8.4
Vomiting	7	4.3	2	1.3	9	2.8
INFECTIONS AND INFESTATIONS	36	22.2	33	20.6	69	21.4
Urinary Tract Infection	4	2.5	9	5.6	13	4.0
Bronchitis	1	0.6	3	1.9	4	1.2
Cystitis	4	2.5	0	0.0	4	1.2
Nasopharyngitis	8	4.9	4	2.5	12	3.7
Lower Respiratory Tract Infection	3	1.9	3	1.9	6	1.9
Gastroenteritis	3	1.9	3	1.9	6	1.9
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	28	17.3	21	13.1	49	15.2
Neck Pain	3	1.9	2	1.3	5	1.6
Myalgia	2	1.2	3	1.9	5	1.6
Back Pain	5	3.1	7	4.4	12	3.7
Arthralgia	5	3.1	4	2.5	9	2.8
NERVOUS SYSTEM DISORDERS	26	16.0	22	13.8	48	14.9
Dizziness	9	5.6	5	3.1	14	4.3
Headache	6	3.7	5	3.1	11	3.4
Tremor	3	1.9	2	1.3	5	1.6

Overall the incidence of AEs was similar between the two groups. As might be expected with this class of drugs, the most common class of AEs was gastrointestinal: a total of 79 subjects (24.5%) in the study experienced gastrointestinal AEs. Nausea, diarrhoea and dizziness were the three most common AEs in the OxyPR group and nausea, diarrhoea and urinary tract infection were the three most common adverse events in the OXN PR group. There were fewer gastrointestinal AEs in the OXN PR group.

A slightly higher number of subjects in the OxyPR group experienced AEs of severe intensity compared to the OXN PR group (21 [13.1%] subjects with 39 severe AEs vs 14 [8.6%] subjects with 32 severe AEs, respectively).

Relationship to Study Drug

The incidence of AEs considered by the investigator to be related to study drug was similar between the two groups (60 [37.5%] subjects with 149 related AEs in the OxyPR group vs 57 [35.2%] subjects with 148 related AEs in the OXN PR group). In both treatment groups the number of subjects with related SAEs was very low (4 [2.5%] subjects with 5 related AEs in the OxyPR group vs 1 (0.6%) subject with 2 related AEs in the OXN PR group). The number of related gastrointestinal AEs was 37 (23.1%) subjects with 57 related AEs in the OxyPR group vs 24 (14.8%) subjects with 33 related AEs in the OXN PR group.

Serious Adverse Events and Deaths

In the Double-blind Safety Population 12 subjects experienced serious adverse events (SAEs); 9 in the OxyPR group and 3 in the OXN PR.

Five subjects experienced 7 SAEs for which the investigator suspected a causal relationship to study medication. In the OxyPR group, 5 related SAEs were reported in 4 subjects (cellulitis, cerebrovascular accident, gastrointestinal haemorrhage each in one subject; lumbar radiculopathy and cerebrovascular accident in one patient). In the OXN PR group, 2 related SAEs were observed in one subject (drug withdrawal syndrome, ECG changes [T-wave changes]). Causal relationship to study drug was rated “unlikely”, or “not related” for the majority of these SAEs .

There were no deaths reported in the core phases of study OXN3001.

Adverse Events Leading to Study Withdrawal

Overall, the incidence of AEs leading to discontinuation during Double-blind Phase was low. 27 subjects in the OXN PR group and 31 subjects in the OxyPR group discontinued due to AEs. The AEs, which most frequently led to discontinuation for the Double-blind Safety Population, were diarrhoea (n = 5, 1.25% of subjects; 2 in the OxyPR group and 3 in the OXN PR group), constipation (n = 4, 1.24% of subjects; all of whom were in the OxyPR group), and nausea (n = 4, 1.24% of subjects; 3 in the OxyPR group and 1 in the OXN PR group). One subject was discontinued from the study in the OXN PR group reporting drug withdrawal syndrome and ECG changes, which were both considered probably causally related to the study drug.

Adverse Events of Special Interest

Gastrointestinal AEs

Overall, there were fewer gastrointestinal AEs reported in the OXN PR group. The number of related gastrointestinal AEs was also lower in the OXN PR group. 20 subjects experienced diarrhoea which was generally transient in duration, and rates were comparable between groups (11 in OxyPR group, 9 in OXN PR). The number of related diarrhoeas was slightly higher in the OXN PR group (8 in 7 subjects [4.3%] compared to the OxyPR group (6 in 4 subjects [2.5%]). The mean duration of treatment-related diarrhoea was slightly lower in the OXN PR group than in the OxyPR group (6.13 days in the OXN PR group vs 7 days in the OxyPR group).

Opioid Withdrawal

Two subjects had AEs that were considered by the investigator to be related to opioid withdrawal, one in each treatment group. One subject in the OxyPR group experienced an AE of opioid withdrawal that was probably related to study drug. She had been taking 30 mg OxyPR for 37 days at the time of the event. No action was taken and the event was ongoing at the end of study. One subject in the OXN PR group experienced opioid withdrawal with ECG changes that were considered by the investigator to be medically significant (serious) and probably related to study medication. She had been taking 40 mg OXN PR for 3 days at the time of the event. The subject recovered after study medication was stopped.

Clinical Laboratory Evaluations

The majority of the clinical laboratory values were normal at baseline and at the end of the study. Analysis of shifts from Run-in to end of the Double-blind Phase revealed no shift of clinical concern for haematology or blood chemistry. There were no important differences between the treatment groups in abnormal laboratory parameters and no major safety signals were observed in either group.

Study OXN3006

Extent of Exposure

During the Double-blind Phase, 135 subjects were exposed to OxyPR and 130 subjects were exposed to OXN PR. The majority of subjects received study medication for 12 weeks (≥ 84 days). 83.7% of subjects in the OxyPR group and 82.3% of subjects in the OXN PR group received study medication for ≥78 days (approximately ≥11 weeks). Mean (SD) duration of exposure was similar in both treatment groups (77.6 days (23.11) in the OxyPR group and 76.1 days (22.57) in the OXN PR group). The maximum duration was 106 days in the OxyPR group and 101 days in the OXN PR group (approximately 14 weeks). The overall mean daily doses of OxyPR and OXN PR were 71.9 mg (14.81) and 74.4 (13.57) mg, respectively. The number of subjects who received the same dose of study medication at the end of the Double-blind Phase compared to randomisation were similar in both treatment groups.

The mean duration of periods in which subjects received a dose of more than 80 mg oxycodone PR per day was at least 30 days. In general subjects received a dose of more than 80 mg OxyPR for a minimum of 8 days and up to a maximum of 84 days.

Adverse Events (AEs)

An overview of AEs in the Double-blind Phase is provided in Table 8. The overall number of AEs and related AEs was higher in the OXN PR treatment group compared to the OxyPR group. There were also a higher number of subjects with severe (11.5% vs 9.6%) AEs in the OXN PR group compared to the OxyPR group.

Table 8: Study OXN3006 - Overview of Adverse Events: Double-Blind Phase - Double-blind Safety Population

	OxyPR		OXN PR		Total	
Category	(N=135)	%	(N=130)	%	(N=265)	%
Number of AEs	173		213		386	
Number of subjects with AEs	71	52.6	82	63.1	153	57.7
Number of related AEs	83		120		203	
Number of subjects with related AEs	40	29.6	49	37.7	89	33.6
Number of severe AEs	17		27		44	
Number of subjects with severe AEs	13	9.6	15	11.5	28	10.6
Number of SAEs	6		15		21	
Number of subjects with SAEs	6	4.4	10	7.7	16	6.0
Number of related SAEs*	1		10		11	
Number of subjects with related SAEs*	1	0.7	6	4.6	7	2.6

Reference: [see CSR OXN3006, section 12.1, Table 41]
* Considered to be related by the Investigator

Common Adverse Events

Table 9 summarises the common AEs, those with an SOC incidence of ≥10% and preferred term incidence of ≥1% in any treatment group, by MedDRA term. The incidence of AEs was higher in the OXN PR treatment group (63.1%) compared to the OxyPR group (52.6%). The most frequently reported AEs were abdominal pain (10 [7.7%]), nausea (13 [10.0%]), pain (10 [7.7%]) and headache (7 [5.4%]) in the OXN PR group and nausea (9 [6.7%]), pain (5 [3.7%]), back pain (5 [3.7%]) and headache (5 [3.7%]) in the OxyPR group. The majority of AEs were considered to be of mild or moderate intensity.

Relationship to Study Drug

The incidence of AEs considered by the investigator to be related to study drug was higher in the OXN PR treatment group compared to the OxyPR group: 40 (29.6%) subjects with 83 related adverse events in the OxyPR group vs 49 (37.7%) subjects with 120 related adverse events in the OXN PR group). The number of subjects with related SAEs was 1 (0.7%) subject with 1 related SAE in the OxyPR group versus 6 (4.6%) subjects with 10 related SAEs in the OXN PR group.

Subgroup Analysis of Subjects Taking > 80 mg Oxycodone PR per Day for > 7 days

A higher number of AEs (49 vs 28) and related AEs (37 vs 21) were reported in the OXN PR treatment group compared to the OxyPR group. There was also a higher number of subjects with severe (15.4% vs 10.5%) and serious adverse events (7.7% vs 0.0%) in the OXN PR group than in the OxyPR group, respectively. However, the number of subjects with related AEs was higher in the OxyPR group compared to the OXN PR group (57.9% vs 53.8%).

The patterns and incidences of common AEs in the subgroup analysis were similar to those seen in the general population.

Serious Adverse Events and Deaths

SAEs were reported for 16 subjects: 6 in the OxyPR group and 10 in the OXN PR group. In the Double-blind phase 7 subjects experienced 11 SAEs for which the investigator suspected a causal relationship to study medication: one SAE in 1 subject in the OxyPR group (1 unlikely related cholelithiasis) and 10 SAEs in 6 subjects in the OXN PR group (5 SAEs unlikely to be related in 3 subjects). Events included angina pectoris, thrombosis, thrombophlebitis superficial, nausea, headache, skin laceration, grand mal convulsion, right bundle branch block, pneumonia and choledocholithisasis with obstruction of the bile duct. The right bundle branch block was considered

'unlikely related', and indeed for the majority of SAEs the causality was rated 'unlikely' or 'not related'. There were no deaths reported in the core phases of study OXN3006.

Table 9: Study OXN3006 - Incidence of Adverse Events by System Organ Class (≥10%) and Preferred Term (≥1%): Double-blind Safety Population

MedDRA System Organ Class[a] MedDRA Preferred Term	OxyPR (N=135)	%	OXN PR (N=130)	%	Total (N=265)	%
Any AE	71	52.6	82	63.1	153	57.7
Gastrointestinal disorders	22	16.3	31	23.8	53	20.0
Abdominal pain	2	1.5	10	7.7	12	4.5
Abdominal pain upper	3	2.2	4	3.1	7	2.6
Constipation	2	1.5	1	0.8	3	1.1
Diarrhoea	4	3.0	6	4.6	10	3.8
Dry mouth	2	1.5	1	0.8	3	1.1
Nausea	9	6.7	13	10.0	22	8.3
Vomiting	1	0.7	4	3.1	5	1.9
General disorders and administration site conditions	16	11.9	21	16.2	37	14.0
Chest pain	1	0.7	2	1.5	3	1.1
Chills	2	1.5	3	2.3	5	1.9
Drug withdrawal syndrome	4	3.0	0	0.0	4	1.5
Fatigue	4	3.0	2	1.5	6	2.3
Feeling cold	0	0.0	3	2.3	3	1.1
Pain	5	3.7	10	7.7	15	5.7
Infections and infestations	23	17.0	15	11.5	38	14.3
Gastroenteritis	4	3.0	2	1.5	6	2.3
Influenza	4	3.0	1	0.8	5	1.9
Nasopharyngitis	3	2.2	1	0.8	4	1.5
Sinusitis	2	1.5	2	1.5	4	1.5
Urinary tract infection	2	1.5	4	3.1	6	2.3
Musculoskeletal and connective tissue disorders	10	7.4	19	14.6	29	10.9
Arthralgia	1	0.7	2	1.5	3	1.1
Back pain	5	3.7	5	3.8	10	3.8
Osteoarthritis	3	2.2	1	0.8	4	1.5
Nervous system disorders	13	9.6	19	14.6	32	12.1
Dizziness	2	1.5	1	0.8	3	1.1
Headache	5	3.7	7	5.4	12	4.5
Sciatica	0	0.0	5	3.8	5	1.9

Reference: [see CSR OXN3006, section 12.1, Table 42]
[a] System Organ Class values are representative for all AEs for that particular System Organ Class (i.e. the values will not be cut by any n% of the subjects).
Note: System Organ Class and MedDRA Preferred Term within System Organ Class are listed alphabetically.

Adverse Events Leading to Study Withdrawal

Seven subjects in each group discontinued due to AEs. The AEs (7 AEs reported in 3 subjects) that most frequently led to discontinuation in the OXN PR group were gastrointestinal, including abdominal pain, diarrhoea, flatulence, and dry mouth. Nervous system AEs leading to study withdrawal were also frequently reported in the OXN PR group and included dizziness (2 subjects) and grand mal convulsion and headache each (1 subject). 2 subjects in the OxyPR group, discontinued due to AEs that included constipation, nausea and diarrhoea. Other AEs that led to study discontinuation in the OxyPR group were restless legs syndrome, paraesthesia and general disorders and administration site conditions, including drug withdrawal syndrome, pain, chills.

Adverse Events of Special Interest

Gastrointestinal AEs

The number of subjects with gastrointestinal AEs was higher in the OXN PR treatment group (23.8%) compared to the OxyPR group (16.3%). The number of subjects with related gastrointestinal AEs was also higher in the OXN PR treatment group (19.2%) compared to the OxyPR group (12.6%). However, the incidence of gastrointestinal SAEs was low: only 1 subject (0.8%) in the OXN PR treatment group experienced a gastrointestinal SAE.

The number of subjects (N=10) reporting diarrhoea was generally low and transient in duration and comparable between groups (4, OxyPR group; 6, OXN PR group).

In the subgroup analysis of subjects taking >80 mg oxycodone PR per day for > 7 days 4 subjects in the OXN PR group experienced gastrointestinal AEs, whereas in the OxyPR group 3 subjects experienced gastrointestinal AEs.

Opioid Withdrawal

Four subjects had AEs that were considered by the investigator to be related to opioid withdrawal, and all of occurred in the OxyPR group.

Clinical Laboratory Evaluations

The majority of the clinical laboratory values were normal at baseline and at the end of the study. Analysis of shifts from Run-in to end of the Double-blind Phase revealed no shift of clinical concern for haematology or blood chemistry, and there were no important differences between the treatment groups in abnormal laboratory parameters.

Study OXN3401

Extent of Exposure

During the Double-blind Phase, 158 subjects were exposed to placebo, 151 subjects were exposed to oxycodone and 154 subjects were exposed to oxycodone/naloxone]. The mean duration of exposure to 20 mg study drug was similar in all treatment groups (total mean 79.63 days). The mean duration of exposure to 40 mg of placebo (70.64 days) was decreased in comparison to 40 mg of oxycodone (75.81 days) or oxycodone/naloxone (75.74 days), which was probably due to the higher drop-out rate in this group. The majority of subjects received study treatments for at least 84 days. The maximum duration of exposure was 123 days in the 20 mg oxycodone/naloxone treatment group and 106 days in the 40 mg oxycodone treatment group.

Adverse Events (AEs)

Table 10 provides an overview of AEs in the Double-blind Phase. The percentage of subjects with AEs was comparable across all treatment groups. The number of related AEs was highest in the OxyPR group (152) followed by the placebo (138) and OXN PR (118) group. Overall 10 subjects experienced 24 SAEs, a relatively high number that may have been due to the reporting strategy (SAEs were defined as all signs and symptoms reported by the investigator and each individual sign and symptom were regarded as an SAE). The percentage of subjects with related SAEs was higher in the OXN PR (2.6%) compared to the OxyPR (0.0%) and placebo (0.6%) groups.

Table 10: Study OXN3401 – Overview of Adverse Events: Double-blind Safety Population

	Placebo (N = 158)	OxyPR (N = 151)	OXN PR (N = 154)	Total (N = 463)
	N (%)	N (%)	N (%)	N (%)
Number of Subjects with AEs	83 (52.5)	80 (53.0)	86 (55.8)	249 (53.8)
Number of AEs	236	226	222	684
Number of Related AEs	138	152	118	408
Number of AEs Leading to Discontinuation	25	7	15	47
Number of Subjects with AEs Leading to Discontinuation	13 (8.2)	4 (2.6)	6 (3.9)	23 (5.0)
Number of SAEs	3	1	20	24
Number of Subjects with SAEs	3 (1.9)	1 (0.7)	6 (3.9)	10 (2.2)
Number of Related SAEs	1	0	12	13
Number of Subjects with Related SAEs	1 (0.6)	0 (0.0)	4 (2.6)	5 (1.1)

According to sponsor's assessment: 2 related SAEs and 2 subjects with related SAEs with placebo, 15 related SAEs with oxycodone/naloxone

Common Adverse Events

Table 11 presents the incidence of AEs reported in ≥ 2% of subjects by System Organ Class and Preferred Term (MedDRA) for the Double-blind Safety Population. Overall, the incidence of AEs during the Double-blind Phase was comparable between the different treatment groups (placebo 52.5%, OxyPR 53.0% and OXN PR 55.8%). Constipation, nausea, headache, vomiting and diarrhoea were the most frequently reported AEs during the Double-blind Phase. The incidence of constipation was highest in the OxyPR group (11.9%). Overall, most AEs were mild or moderate and the incidence of AEs reported with a severe intensity was low.

Relationship to Study Drug

Subjects receiving OxyPR showed a higher incidence of AEs considered by the investigator to be related to study drug (n=152) compared with subjects receiving OXN PR (n=118) and placebo (n=138).

Serious Adverse Events and Deaths

Overall 24 SAEs were reported. In the double-blind phase there were 13 SAEs with a suspected causal relationship to study medication; one in the placebo and twelve in the OXN PR group. In ten of the thirteen SAEs the causal relationship to study drug was rated "unlikely" and therefore probably not related to the safety profile of OXN PR. Three cases in two subjects were assessed as possibly related by the investigator; one case of fall, one case of drop in blood pressure to 95/55mmHg, and one case of confusion, nausea, abdominal pain and vomiting. These SAEs are possibly related to study drug.

In Study OXN3401, one subject died during the run-in period of the study. The female patient had received OxyIR for titration purposes and died during the pre-randomisation phase from instantaneous cardiac death. The subject had not received OXN PR at the time of death and the death was not considered to be related to the study drug OxyIR.

Table 11: Study OXN3401 - Incidence of Adverse Events Reported in ≥ 2% of Subjects by System Organ Class and Preferred Term (MedDRA): Double-blind Safety Population

	Placebo (N = 158)	OxyPR (N = 151)	OXN PR (N = 154)	Total (N = 463)
System Organ Class / Preferred Term	N (%)	N (%)	N (%)	N (%)
Overall Incidence of Adverse Events	83 (52.5)	80 (53.0)	86 (55.8)	249 (53.8)
Ear and Labyrinth Disorders				
Vertigo	5 (3.2)	5 (3.3)	2 (1.3)	12 (2.6)
Gastrointestinal Disorders				
Constipation	8 (5.1)	18 (11.9)	13 (8.4)	39 (8.4)
Diarrhoea	7 (4.4)	4 (2.6)	8 (5.2)	19 (4.1)
Dyspepsia	3 (1.9)	7 (4.6)	3 (1.9)	13 (2.8)
Nausea	11 (7.0)	12 (7.9)	10 (6.5)	33 (7.1)
Vomiting	5 (3.2)	7 (4.6)	8 (5.2)	20 (4.3)
General Disorders and Administration Site Conditions				
Fatigue	4 (2.5)	8 (5.3)	4 (2.6)	16 (3.5)
Infections and Infestations				
Nasopharyngitis	4 (2.5)	5 (3.3)	2 (1.3)	11 (2.4)
Investigations				
Blood Triglycerides Increased	3 (1.9)	5 (3.3)	3 (1.9)	11 (2.4)
Nervous System Disorders				
Dizziness	6 (3.8)	9 (6.0)	2 (1.3)	17 (3.7)
Headache	11 (7.0)	6 (4.0)	5 (3.2)	22 (4.8)
Skin and Subcutaneous Tissue Disorders				
Hyperhidrosis	7 (4.4)	2 (1.3)	5 (3.2)	14 (3.0)
Pruritus	4 (2.5)	3 (2.0)	5 (3.2)	12 (2.6)

Adverse Events Leading to Study Withdrawal

Overall, 23 subjects (5%) withdrew from the study due to AEs (n=47). The number of AEs leading to discontinuation was comparable between the OxyPR and OXN PR group. The AEs which most frequently led to discontinuation for the double-blind safety population were nausea (n = 8, 1.73% of subjects), vertigo/dizziness (n = 5, 1.08% of subjects), vomiting and headache (n = 4, 0.86% each).

Adverse Events of Special Interest

Gastrointestinal *AEs*

The number of subjects with gastrointestinal AEs was comparable across all treatment groups with slightly higher numbers in the OxyPR treatment arm. The number of gastrointestinal AEs related to study drug was also highest in the OxyPR group (58). The number of subjects experiencing diarrhoea was generally low in all treatment groups, and the incidence of diarrhoea was comparable across all treatment groups.

Opioid Withdrawal

One subject in the placebo group reported drug withdrawal syndrome which was probably due to the lack of regular opioid intake. Throughout the Double-blind Phase mean opiate withdrawal scores were stable, low and comparable in all treatment groups.

Clinical Laboratory Evaluations

The majority of the clinical laboratory values were normal at baseline and at the end of the study. The shift analysis revealed no shift of clinical concern for haematology or clinical chemistry parameters.

Study OXN3401S

Extent of Exposure

333 subjects received OXN PR for at least 6 months and 277 subjects received OXN PR for at least 12 months.

Adverse Events (AEs)

Table 12 provides an overview of AEs in the Extension Population. Overall 882 AEs were reported in 259 subjects (68%), and 325 of these events in 143 subjects (38%) were considered related to study drug.

Common Adverse Events

Table 13 presents the incidence of AEs reported in ≥ 2% of subjects by System Organ Class and Preferred Term for the Extension Population. Overall, the incidence of AEs during the Extension Phase (68%) was comparable to the core phase (OXN PR 55.8%, OxyPR 53.0%, placebo 52.5%), taking into consideration the longer observation period of 12 months. Constipation (n=35; 9.2%), nausea (n=29; 7.7%), back pain (n=24; 6.3%) and depression (n=24; 6.3%) were the most frequently reported adverse events. Constipation and nausea are expected adverse effects of treatment with a strong opioid; back pain and depression may be related to the underlying medical condition. Most AEs were mild or moderate and the incidence of severe AEs was low (13%).

Table 12: Study OXN3401S - Overview of Adverse Events: Extension Population

Category	Total (N=379)
Number of AEs	882
Number of Subjects with AEs	259 (68%)
Number of related AEs	325
Number of Subjects with related AEs	143 (38%)
Number of AEs Leading to Discontinuation	43
Number of Subjects with AEs Leading to Discontinuation	22 (5.8%)
Number of SAEs	90
Number of Subjects with SAEs	49 (13%)
Number of related SAEs*	27
Number of Subjects with related SAEs*	12 (3.2%)

* As assessed by the investigator

Table 13: Study OXN3401S - Incidence of Adverse Events Reported in ≥ 2% of Subjects by System Organ Class and Preferred Term (MedDRA): Extension Population

System Organ Class[a] MedDRA Term	Total (N=379) n (%)
Any Adverse Event	259 (68%)
Cardiac Disorders	20 (5.3%)
Ear And Labyrinth Disorders	16 (4.2%)
Vertigo	14 (3.7%)
Gastrointestinal Disorders	**138 (36%)**
Constipation	35 (9.2%)
Nausea	29 (7.7%)
Diarrhoea	12 (3.2%)
Abdominal Pain Upper	9 (2.4%)
Dyspepsia	9 (2.4%)
General Disorders And Administration Site Conditions	41 (11%)
Fatigue	13 (3.4%)
Hepatobiliary Disorders	9 (2.4%)
Infections And Infestations	**102 (27%)**
Nasopharyngitis	20 (5.3%)
Bronchitis	9 (2.4%)
Sinusitis	9 (2.4%)
Injury, Poisoning And Procedural Complications	28 (7.4%)
Investigations	60 (16%)
Weight Decreased	9 (2.4%)
Blood Triglycerides Increased	8 (2.1%)
Metabolism And Nutrition Disorders	32 (8.4%)
Musculoskeletal And Connective Tissue Disorders	**112 (30%)**
Back Pain	24 (6.3%)
Osteoarthritis	14 (3.7%)
Arthralgia	13 (3.4%)
Shoulder Pain	8 (2.1%)
Nervous System Disorders	64 (17%)
Headache	11 (2.9%)
Dizziness	9 (2.4%)
Psychiatric Disorders	49 (13%)
Depression	24 (6.3%)
Insomnia	9 (2.4%)
Renal And Urinary Disorders	15 (4.0%)
Reproductive System And Breast Disorders	14 (3.7%)
Respiratory, Thoracic And Mediastinal Disorders	11 (2.9%)
Skin And Subcutaneous Tissue Disorders	46 (12%)
Hyperhidrosis	20 (5.3%)
Vascular Disorders	25 (6.6%)
Hypertension	10 (2.6%)

Reference: [see CSR OXN3401S, section 5.3.5.2, Table 17]

[a] System organ class values are representative for all adverse events for that particular system organ class (i.e. the values are not cut by any n% of the subjects).
Note: System organ class is listed alphabetically and MedDRA term is listed in descending order of frequency within each system organ class.

Relationship to Study Drug

The incidence of AEs considered by the investigator to be related to study drug (38%) and the number of AEs leading to discontinuation was low (5.8%).

Serious Adverse Events and Deaths

49 subjects (13%) experienced 90 SAEs. 12 subjects experienced 27 SAEs with a suspected causal relationship to study medication, according to the investigators. In 21 of the 27 SAEs, the causal relationship to study drug was rated "unlikely". Six cases in 3 subjects were assessed as being possibly related by the investigator.

Only 3 gastrointestinal SAEs in 3 subjects were rated as being related to study drug.

In the Extension study OXN3401S, 1 subject died 213 days after study medication was started. The cause of death was suffocation due to thoracic compression from a quadricycle accident. The investigator found the AE to be not related to study medication.

Adverse Events Leading to Study Withdrawal

The incidence of AEs leading to discontinuation during the Extension Phase was low. 143 AEs led to discontinuation in 24 subjects (6.2%), and the most frequent reason for discontinuation was nausea (n = 3).

Adverse Events of Special Interest

Gastrointestinal AEs

The incidence of gastrointestinal AEs in the Extension Phase (28%) was comparable to the core phase (24.4%). Constipation (9.2%) and nausea (7.7%) were reported most frequently. Only 3 gastrointestinal SAEs were rated as being related to the study drug.

Opioid Withdrawal

Two subjects reported an adverse event related to opioid withdrawal. In both cases the withdrawal started after the end of study medication intake and therefore was probably related to the change of opioid treatment

Clinical Laboratory Evaluations

The majority of the clinical laboratory values were normal at baseline and at the end of the study. The shift analysis revealed no shift of clinical concern for haematology or clinical chemistry parameters.

Study OXN2401

Extent of Exposure

The duration of exposure to oxycodone plus naloxone was planned to be 4 weeks. During the study, 202 patients received OxyPR plus naloxone PR or corresponding placebo. Mean duration (days) of exposure to either OxyPR or naloxone PR was similar in all dose ratios. Patients in the 60 mg/placebo dose ratio recorded the longest exposure to OxyPR (mean 51.3 days) whilst those in the 1.5/1 dose ratio recorded the shortest exposure (mean 41.0 days). No relevant differences were seen between the mean duration of exposure to either OxyPR or naloxone PR by absolute dose of naloxone PR.

Adverse Events (AEs)

The number of patients experiencing any AE during the maintenance phase was comparable by absolute dose of naloxone PR and placebo (range 62.7% - 70%). No relationship to dose ratio could

be identified; there was a relatively large variation in the incidence of AEs between individual dose ratios (range 47.1% - 88.9%).

Common Adverse Events

The most frequently reported SOC affected was gastrointestinal disorders (92 patients, 45.5%). A trend towards increased incidence within this SOC with increasing naloxone PR dose was seen. The incidence of gastrointestinal disorders was higher among those patients receiving the higher of each dose of naloxone PR in the same oxycodone/naloxone dose ratio groups.

Sweating increased (51 patients, 25.2%), diarrhoea (46 patients, 22.8%), nausea, abdominal pain, restlessness, muscle cramps, sedation, headache and vertigo were the most frequent AEs. The only major difference between dose ratio treatment groups was in the incidence of diarrhoea: 50% in the 1.5/1 dose ratio group and 29.4% in the 2/1 dose ratio group. Most AEs were mild or moderate and the incidence of severe AEs was low.

Relationship to Study Drug

The number of patients experiencing any causally related AE during the maintenance phase ranged from 50% - 60% and there was a trend towards a higher number of patients experiencing causally related events with increasing naloxone PR dose (25 [50.0%], 26 [51.0%], 27 [52.9] and 39 [60.0%] for placebo, 10 mg, 20 mg and 40 mg naloxone PR groups, respectively. No clear relationship to dose ratio could be identified, with there being a relatively large variation in the incidence of causally related AEs between individual dose ratios (range 35.3% - 66.7%). The incidence of causally related SAEs was low; 3 and 2 in the 10 mg and 40 mg naloxone treatment groups respectively. Abdominal pain, diarrhoea, nausea, vertigo, muscle cramps, sedation, restlessness and sweating increased were the most frequent causally-related AEs reported for the active naloxone PR treatment groups.

Serious Adverse Events and Deaths

The incidence of SAEs was generally comparable across all treatment groups: 1 patient (2.0%) in the placebo, 3 patients (5.9%) in the 10 mg, 1 patient (2.0%) in the 20 mg and 3 patients (6.0%) in the 40 mg naloxone treatment groups. There were no deaths reported in study OXN2401.

Adverse Events Leading to Study Withdrawal

Of the 36 subjects who discontinued from the study during the maintenance phase, 22 subjects discontinued due to AEs including signs of withdrawal. All eight subjects with SAEs discontinued from the study. The frequency of discontinuations due to AEs during the maintenance phase increased with an increasing dose of naloxone PR: 1 patient (2.0%), 5 patients (9.8%), 6 patients (11.8%) and 9 patients (18.0%) for the placebo, 10 mg, 20 mg and 40 mg naloxone PR treatment groups respectively. The major reasons for discontinuation in the naloxone PR 20 mg and 40 mg treatment groups were gastrointestinal disorders. No other AE leading to discontinuation occurred in more than 10% of all patients in any treatment group. The highest proportion of patients with AEs leading to discontinuation (5 patients, 27.8%) occurred with the dose ratio 3/1.

Clinical Laboratory Evaluations

No trends or treatment changes of note were reported.

Clinical Pharmacology Studies

Extent of Exposure

Overall, 366 subjects received the study drug in the clinical pharmacology studies. The majority of the studies were single-dose crossover trials with 3-5 treatment periods. Two studies were multiple-dose studies (OXN1011 and OXN1017), in which subjects were administered study drug for a

duration of 3.5 days (7 doses). The OXN10/5 mg PR and OXN20/10 mg PR doses were the most often administered doses in most studies.

Adverse Events (AEs)

Common Adverse Events

Overall the AEs reported were typical of opioid treatment in opioid naive subjects. In healthy subjects the most frequently reported AEs were nausea and vomiting, headache, dizziness and somnolence.

Serious Adverse Events and Deaths

One subject experienced 2 SAEs during OXN20/10 "fast" treatment in Study OXN1013. On the first day of treatment the subject experienced five episodes of vomiting and palpitations that were confirmed as being due to atrial fibrillation by ECG. The subject subsequently recovered; however was withdrawn from the study.

Clinical Laboratory Evaluations

No trends or treatment changes of note were reported.

Overdose, Drug Abuse, Withdrawal and Rebound

Symptoms of oxycodone hydrochloride overdose may include respiratory depression, somnolence, progressing to stupor or coma, skeletal muscle flaccidity, miotic pupils, bradycardia, hypotension and death. As OXN prolonged-release tablets contain naloxone hydrochloride also, observation of these symptoms might be delayed.

Clinical symptoms indicating an overdose of oxycodone hydrochloride may be treated by the administration of opioid receptor antagonists (for example, naloxone hydrochloride 0.4-2 mg intravenously).

The safety profile of oxycodone is similar to that of other opioid analgesics, and includes the potential for the development of psychological dependence as well as of drug abuse or intentional misuse. Because of the presence of naloxone in the combination tablet, the risk of psychological dependence to, as well as abuse and diversion of, OXN PR tablets is expected to be lower than the risk associated with oxycodone in OxyContin tablets.

As with other opioids there is a risk for withdrawal symptoms after abrupt cessation of high doses or long time administration of oxycodone. The sponsor has stated that it is not known at this time whether and to which extent the presence of naloxone in OXN PR will alter withdrawal symptoms.

Summary of Safety

Overall OXN PR is generally well tolerated. AEs reported in the clinical trials primarily affected the gastrointestinal system. The most frequently reported AEs were dizziness, nausea, headache, vomiting, and diarrhoea. Constipation was observed in a frequency between 1% and 10% ("common") which is expected due to the fact that OXN PR contains a strong opioid. However, the observed frequency of constipation is still far below of that of oxycodone alone. The number of subjects reporting gastrointestinal AEs was similar across all treatment groups.

There were no deaths considered drug-related in clinical trials, and the majority of SAEs were considered not related to study drug. There were relatively few cases of withdrawal syndrome. There were no clinically relevant safety signals detected from review of clinical laboratory tests and vital signs. No new or additional safety concerns became apparent following longer-term use of OXN PR.

The evaluator noted that overall the data presented for evaluation support the use of OXN PR and confirmed that the safety profile is similar to monotherapy with OxyPR but improved for

constipation, and with a reduced potential for drug abuse. Safety assessments for Phase III studies did not signal any specific safety risks or issues when uptitrating the total daily dose up to 120/60 mg OXNPR.

Post-marketing Experience

The sponsor provided post-marketing data in three Periodic Safety Update Reports (PSURs) for the reporting periods 31 March 2006 to 30 September 2007 and from study OXN9002.

November 2006 PSUR

As OXN PR was first marketed in Germany after the time period covered by this PSUR (31 March 2006 – 30 September 2006), at this time the drug was only used in clinical trials. During the reporting period, approximately 1500 subjects were enrolled in clinical trials involving OXN PR.

Overall 14 case reports were received from 5 countries. One case was rated as "serious listed". Altogether 36 adverse events occurred in the 14 cases; most ADRs are rated under the gastrointestinal disorders (n=9) and the nervous system disorders SOC (n=5). All the case reports contained in this PSUR were from the clinical studies OXN3401, 3001 and 3006.

Two cases with the adverse drug reaction of cholecystitis were reported in the report period. In one case it was assessed as being "possibly" related to OXNPR. The sponsor performed a safety analysis identifying four cases of acute cholecystitis, one of cholecystectomy and one of cholelithiasis in the oxycodone / naloxone -studies. All but one of the affected patients had received oxycodone/naloxone as study medication. At the pathophysiological level, opioids, including oxycodone, are known to influence the Sphincter of Oddi tone, causing constriction. If this is combined with mechanical irritation of the gall bladder by pre-existing gall stones, a causal relationship between OXN PR and the resulting inflammatory process is plausible. In light of this the sponsor proposes to include a precaution that oxycodone/naloxone should not be used in patients with pre-existing cholelithiasis in the "Special Warnings and Precautions for Use" section of the product information.

May 2007 PSUR

The second PSUR covered six months (01 October 2006 - 30 March 2007) of post launch data. The total "patient days" of exposure for the single daily dose was 3,235,000 (107,800 patient months) which equals the number of "patient days" and "patient months" of exposure for the twice-daily dose for the 6 months covered by this report. In addition to the post-marketing exposure, approximately 1000 subjects were still enrolled in ongoing clinical trials involving OXN PR in the report period.

Overall 150 case reports were received from 5 countries. 59 of the 150 cases were "serious unlisted" with a total of 101 serious unlisted adverse events. Altogether 324 adverse events occurred in the 150 cases.

There were a total of four cases with a fatal outcome in the report interval, however none were considered related to OXNPR. The following clusters of AEs were observed in the report period, and are proposed for inclusion into the OXN PR product information: visual disturbances, asthenic conditions, chest pain, insomnia, peripheral oedema, paraesthesia, speech disorder, injuries from accidents, anorexia, confusion, abnormal thinking, depression, hallucination, erectile dysfunction, dyspnoea, hypertension (increase in blood pressure).

November 2007 PSUR

This was the third PSUR for oxycodone / naloxone (OXN PR) formulations and includes ADR case reports and other relevant data received by the sponsor for the reporting period 31 March 2007 to 30 September 2007. Units equalling a total of approximately 5.140.000 patient days (approximately

170.000 patient months) were distributed in the reference period for this report. Approximately 500 subjects were still enrolled in ongoing clinical trials involving OXN PR in the reporting period. In addition, study OXN9002 using the marketed product was ongoing during the report period.

Overall 95 case reports were received from five countries, of which 66 constitute initial reports. In total, 39 of the 95 cases were rated as "serious unlisted" with a total of 64 "serious unlisted" adverse events. Altogether 205 adverse events occurred in the 95 cases. The majority of ADRs were rated under nervous system disorders (n=37), gastrointestinal disorders (n=32), psychiatric disorders (n=30), and general disorders and administration site conditions (n=29) SOCs.

One serious case of drug interaction with levodopa was reported. The patient, who had a history of suspected personality disorder, experienced a personality change in the form of schizoid character traits 64 days after starting OXN PR while taking Restex (levodopa/benserazide). OXN PR was continued and Restex was discontinued. The events were ongoing at the time of the report. The reporter considered the AE to be possibly related to OXN PR.

In relation to the German Summary of Product Characteristics (SPC), one variation was filed in the reporting period of this PSUR to include safety issues already addressed in the Executive Summary of the previous PSUR. In addition, a second variation to update the SPC was filed after the data lock point of this PSUR. This variation included two changes:

- addition of a perioperative warning to section 4.4 of the SPC
- the move of three ADRs from the "oxycodone class labelling section" of the product information to the OXN specific part of section 4.8. in the SPC. The ADR terms in question are disturbance in attention, palpitation and malaise.

The sponsor is continuing to monitor cardiovascular AEs, including atrial fibrillation, myocardial infarction and cerebral infarction/cerebrovascular accident. No new cases have been reported.

Observational Study OXN9002

Overall, 7535 "complaints/symptoms" occurred in 3353 patients (42.8% of all patients). The most frequent complaint/symptom prior to therapy with OXN PR was constipation, which was documented in 32.6% of all patients, followed by nausea (21.2%), dizziness (16.3%), and fatigue (12.3%).

In the subgroup of opioid-naïve patients 1019 complaints occurred in 489 patients (24.9%). The highest values were for constipation (13.7% of patients in opioid-naïve patients), nausea (12.6%), dizziness (9.4%), and fatigue (7.0%). In the group of opioid-pre-treated patients 6496 complaints occurred in 2855 patients (48.8%). The highest values were for constipation (39.0% of patients), nausea (24.1%), dizziness (18.7%), and fatigue (14.1%).

The majority of AEs with a documented severity grading were considered to be of mild (50.5%) or moderate (29.3%) intensity. Approximately 20% were classified as severe.

177 (2.3%) of the 7836 patients experienced at least one serious adverse event (SAE); the total count of single SAEs equalled 244. A causal relationship (definite, probable, possible, unlikely or missing) by either the treating physician and/or the sponsor's drug safety department was documented in 51 of these 177 patients (0.7%).

178 patients (2.3%) reported diarrhoea, with a positive causal relationship documented in 148 of the patients. 23 patients (0.3%) reported drug withdrawal syndrome, and a positive causal relationship was documented in 14 of the 23 patients.

Overall, the pattern of AEs reported in OXN9002 is consistent with the safety profile which can be expected for an opioid analgesic.

Clinical Summary and Conclusions

Pharmacokinetic data showed that the absolute bioavailability of naloxone following oral administration was negligible (OXN1019). A significant level of systemic naloxone exposure was attained following intravenous or intra-nasal administration. The oxycodone PK profile from OXN PR was shown to be bioequivalent to OxyPR. The pharmacokinetics of oxycodone and naloxone-3-glucuronide are dose-proportional.

Elderly subjects exhibited higher plasma concentrations of oxycodone and a recommendation that elderly subjects be dosed according to individual conditions and pain severity is proposed.

In renal impairment, the bioavailability of both oxycodone and naloxone was increased. It is therefore recommended that doses should be adjusted to the individual patient's condition and that patients should be observed for symptoms of overdose of either active substance. This is addressed in the proposed PI of OXN PR.

In moderate to severe hepatic impairment, the bioavailability of both oxycodone and naloxone was significantly increased. Consequently, moderate and severe hepatic impairment is a contraindication and is stated as such in the proposed PI.

Caution should be exercised when administering OXN PR tablets for patients with mild hepatic impairment.

The clinical trial programme demonstrated that OXN PR and OxyPR showed similar analgesic efficacy (studies OXN3401, OXN3001 and OXN3006) up to a total daily dose of OXN120/60 PR mg. Results of the meta-analysis (OXN9001) were consistent with this. In addition it was demonstrated in studies OXN3001 and OXN3006 that subjects receiving OXN PR had an improvement in bowel function compared to subjects receiving OxyPR alone. The laxative intake was significantly decreased. Improvement in bowel function was demonstrated in a subgroup of constipated subjects (BFI $\geq$ 50) in study OXN3401 receiving OXN PR compared to OxyPR.

In the clinical programme there were a limited number of patients who received a dose of OXN120/60 PR mg daily. The pivotal efficacy findings in the Phase III studies are supported by the dose finding study OXN2401 and the post-marketing surveillance study OXN9002. In study OXN2401 it was shown that OXN PR and OxyPR provided similar analgesic efficacy. It was also demonstrated that subjects receiving the combination of oxycodone and naloxone in a ratio of 2:1 up to a total daily dose of 80/40 mg had an improvement in bowel function compared to subjects receiving OxyPR alone. After termination of the double-blind phase subjects were switched to a treatment with OxyPR alone within a follow-up phase of 2 weeks, and during this period the BFI value of the subjects increased again. This observation indicates that the naloxone component of OXN PR can be used for the treatment and prophylaxis of opioid-induced constipation. The observational study, OXN9002, demonstrated that OXN PR is an effective analgesic and showed an improvement in bowel function.

Overall OXN PR was shown to be reasonably well tolerated. AEs reported in the clinical trials primarily affected the gastrointestinal system. The most frequently reported AEs were dizziness, nausea, headache, vomiting, and diarrhoea. Constipation was observed in a frequency between 1% and 10% ("common") which is expected due to the fact that OXN PR contains a strong opioid. However, the observed frequency of constipation was well below of that of oxycodone alone. The number of subjects reporting gastrointestinal AEs was similar across all treatment groups.

The majority of SAEs were considered not related to study drug, and there were relatively few cases of withdrawal syndrome. There were no clinically relevant safety signals detected from review of clinical laboratory tests and vital signs. No new or additional safety concerns became apparent following longer-term use of OXN PR.

The safety data presented for evaluation confirmed that the safety profile of OXN PR is similar to monotherapy with OxyPR but improved for constipation, and with a reduced potential for drug abuse. Safety assessments from Phase III studies did signal any specific safety risks or issues when uptitrating the total daily dose up to 120/60 mg OXNPR.

Overall, the evaluator considered that the efficacy data presented for evaluation have adequately demonstrated that OXN PR is an effective opioid analgesic. It has been shown that the naloxone component in fixed combination with oxycodone is effective for the therapy and/or prophylaxis of opioid-induced constipation. The overall risk/benefit profile is favourable.

In the clinical programme a limited number of patients received a dose of OXN120/60 PR mg daily, and therefore it is appropriate that a maximum total daily dose of 80 mg of oxycodone and 40 mg of naloxone (OXN80/40 mg PR) should be recommended for treatment of pain.

On the basis of the data presented for evaluation, the evaluator recommended that the application for marketing authorisation for Targin tablets, containing a fixed combination of oxycodone hydrochloride and naloxone hydrochloride dihydrate in a controlled release should be approved.

The therapeutic indication for Targin should be as proposed by the sponsor.

V. Pharmacovigilance Findings

There was no Risk Management Plan submitted with this application as it was not a requirement at the time of submission.

VI. Overall Conclusion and Risk/Benefit Assessment

The submission was summarised in the following Delegate's overview and recommendations:

Quality

There were no objections on chemistry, manufacturing or quality control grounds to registration of Targin tablets.

Four strengths of modified release tablet are proposed. *In vitro* studies have demonstrated that the rate of release of active ingredients from the tablets is not affected by alcohol.

In study 1403 bioequivalence of a single dose of the three higher strength Targin tablets against single agent oxycodone modified release tablets (Oxygesic tablets) and single agent naloxone modified release tablets given concomitantly was examined. This study showed that the three higher strength tablets were bioequivalent with respect to oxycodone. In view of the low oral bioavailability of naloxone, the most appropriate parameter for comparing different treatments with regard to this component is the level of its primary metabolite, naloxone-3-glucouronide. All 4 treatments were bioequivalent with regard to both AUC and C_{max}.

Nonclinical

There were no nonclinical objections to the registration of Targin. The toxicological profiles of oxycodone and naloxone are well known from previous evaluations and both are registered in other products. The nonclinical evaluator has noted that specific safety pharmacology studies were not performed because of the long history of clinical use for both oxycodone and naloxone. No significant adverse properties of oxycodone/ naloxone dosing were demonstrated by the sponsor's investigations. Studies in key areas indicated: a lack of toxicologically significant findings and a quick resolution of clinical signs after repeat dosing with oxycodone/ naloxone in rats and dogs; the genotoxic potential of both drugs under *in vivo* dosing conditions is low; naloxone is not carcinogenic in rats; and there is no evidence that oxycodone or naloxone are teratogens in rats or rabbits.

Clinical

Pharmacology

Bioavailability and bioequivalence were examined in 9 studies. Three studies compared the PK of oxycodone from Targin with prolonged release formulations of OxyContin and naloxone. Four studies examined the effect of food. There were 2 pharmacodynamic studies, one of these examined the effect on EEG parameters in an experimental pain model and the other examined the effect of 5 mg to 45 mg oral doses of naloxone in antagonising the opioid agonist properties of oxycodone 20 mg.

In study OXN1401, oral doses of naloxone from 5 mg to 45 mg did not alter the AUC or C_{max} of 20 mg oral oxycodone. The pharmacokinetic aspects of this study were inconsistent and pharmacokinetic data from other studies will be referred to in the proposed PI.

This study also measured pain-related evoked cerebral potentials and other measures of pain. After painful stimulation of the nasal mucosa subjects rated the intensity of the perceived pain using a visual analog scale. Concomitantly the EEG was recorded for assessment of pain-related evoked potentials. This study showed a dose-dependent influence of naloxone on amplitude and latency changes caused by oxycodone as an opioid. Based on the 20 mg oxycodone dose, a naloxone dose that didn't significantly influence the analgesic effect of oxycodone would be below 15 mg. Results from this study support the ratio of 2:1 for oxycodone/ naloxone used in Targin.

Study OXN1402 examined the effect of the addition of naloxone at doses from 10 to 100 mg daily to oxycodone on bowel movement and symptoms of withdrawal in methadone stabilised opioid addicts. Naloxone increased the frequency of bowel movements in a dose-dependent manner with an effect seen starting from a naloxone dose of 20 mg daily. Naloxone also induced withdrawal symptoms with a positive correlation between methadone dose and the naloxone dose at which withdrawal occurred ($p= 0.02$). Overall the median dose of naloxone that induced clear symptoms of withdrawal appeared to be 70 mg daily. The onset of bowel movement and withdrawal was usually within the first 6 hours of naloxone administration.

Bioequivalence of the oxycodone component of Targin with oxycodone from Oxygesic tablets (available in Germany) given with a naloxone prolonged release tablet was demonstrated and each of the fixed combination strengths were bioequivalent to each other. There were some differences in T_{max} values with the different strengths. Food (a high fat breakfast) increased the mean C_{max} for oxycodone by 42% from the 5/ 2.5 mg tablet, by 28% from the 10/ 5 mg tablet and by 28% from the 40/ 20 mg tablet. Increases in the C_{max} of oxycodone from OxyContin from 17 to 29% were seen in previously submitted studies and OxyContin may be given without regard to food. Food didn't significantly alter the PK of naloxone.

The PK of oxycodone and naloxone from Targin was examined in the elderly ($\geq$ 65 years) and in patients with hepatic and renal impairment. Compared with adults aged 18 – 45 years the availability of oxycodone was increased by a mean of 18% in elderly subjects. Nearly all this difference was due to the 33% increase for elderly women. The mean increase for elderly men was only 3%. The differences were consistent with differences in renal function in the 2 populations. Naloxone concentrations were also higher in elderly subjects but were variable, with a mean increase of 82% (135% for women). Subjects with moderate and severe hepatic impairment had a 3-fold increase in the bioavailability of oxycodone and a greater than 100 fold increase in bioavailability of naloxone from Targin.

Efficacy

Five studies and a meta-analysis of 2 of those studies were submitted. The sponsor considered 3 studies (OXN3401, OXN3001 and OXN3006) to be pivotal for efficacy. OXN2401 was a Phase 2 study to investigate whether various ratios of oxycodone/ naloxone in combination would lead to

comparable analgesia with an improvement in bowel function compared to oxycodone and placebo in patients with severe chronic pain needing laxatives. Results from this study led to selection of the 2:1 oxycodone/ naloxone preparation for Targin. OXN9002 was a post-market observational study.

Study 3401 was a randomised, double-blind, placebo and active-controlled study to determine safety and efficacy of Targin in subjects with moderate to severe, chronic, non-malignant pain (low back pain). In that study both oxycodone PR and Targin were superior to placebo with respect to time to recurrent pain events for both the ITT and PP populations.

Bowel function was examined using a development Bowel Function Index (BFI) which consisted of 3 questions to measure constipation from the patient's perspective, with patients rating on a 0-10 numerical analogue scale their ease of defecation, feeling of incomplete bowel evacuation and personal judgement regarding constipation. Mean BFIs at randomisation were low in both treatment groups (2.50 and 2.67 for Targin and oxycodone PR respectively) indicating a low proportion of constipated patients enrolled in this study. BFI scores remained low throughout the double-blind period of study for all treatment groups but were lowest in the placebo group. Statistically significant differences in BFI were apparent for the comparisons between placebo and both active treatment groups and between Targin and oxycodone PR.

Studies 3001 and 3006 were randomised, double-blind studies in subjects with non-malignant pain taking Targin compared to oxycodone PR alone. Subjects were required to have constipation secondary to opioid treatment. As with study 3401 there was a screening and run-in period, a 12-week double-blind phase and a 12 month extension phase. At the end of the run-in period subjects with stable pain control and confirmed opioid-related constipation were randomised to Targin or oxycodone PR. Oxycodone IR was provided as rescue medication. Laxatives except for oral Bisacodyl (initially 10 mg daily taken 72 hours after the subjects most recent bowel movement as rescue medication but later amended due to subject discomfort) were not permitted during the run-in and double-blind periods. Subjects taking fibre supplements or bulking agents had to be maintained on a stable dose throughout study.

The primary objectives of these studies were to measure improvement in symptoms of constipation within 4 weeks as indicated by BFI scores. The meta-analysis of these studies had the primary objective of demonstrating non-inferiority of analgesic effect using a pain intensity scale which assessed subjects average pain over 24 hours on a numeric analogue scale from 0 to 10 (0= no pain, 10 = pain as bad as you can imagine) was also measured (clinical summary). BFI scores were presented using a 0-100 analogue scale rather than the 0-10 scale used in study 3401. Validation of the BFI confirmed that changes in the BFI score of > 12 can be regarded as clinically relevant in symptoms of opioid induced constipation. Secondary endpoints included rescue medication intake, patient bowel function measures (stool frequency and consistency and laxative intake) at 4 weeks and BFI at 4 weeks.

A total of 525 subjects were enrolled in study 3001 with 322 randomised to the double-blind phase. Mean BFI scores at screening were 57.5 for the oxycodone PR group and 58.1 for the Targin group. Mean pain intensity score was 5.6 in both groups. 347 subjects were enrolled in study 3006 with 278 randomised to treatment. 13 subjects were then excluded because subject questionnaires were filled-out by investigator site personnel. Mean BFI scores at screening were 64.09 for oxycodone PR and 67.40 for Targin. Mean pain intensity was 5.2 for oxycodone PR and 5.3 for Targin. In study 3001 Targin doses of 20 to 50 mg oxycodone PR were permitted and in study 3006 doses up to 120 mg oxycodone PR daily were permitted.

In both studies there were marked reductions in BFI in the Targin group which were apparent within 7 days of commencing treatment. Both studies showed statistically and clinically

meaningful improvement in bowel function in subjects given Targin compared with those given oxycodone PR.

In the meta-analysis of these studies the non-inferiority bound for pain intensity was taken as 0.8 for the 11 point (0 – 10) scale. This was based on published papers referring to minimum clinical relevant differences regarding superiority of between 1.74 and 3.00. Half the smallest superiority margin was taken as the non-inferiority margin. Analgesic effect was well maintained in both treatment groups with mean pain intensity scores between 3.3 and 3.7 throughout the 12-week double-blind period of the study in both groups. Non-inferiority of Targin with oxycodone PR was demonstrated - difference 0.08 (CI -0.07 to 0.23) $p < 0.0001$. Use of supplemental analgesia was similar in the treatment groups with mean daily use of 0.7 in the oxycodone PR group and 0.8 in the Targin group.

The highest dose of Targin was given in study 3006 where doses of oxycodone to 120 mg daily were permitted. The mean daily double-blind dose of Targin in this study was 74.4 mg. A subgroup analysis of efficacy with respect to BFI was performed for subjects who received >80 mg oxycodone daily for more than 7 consecutive days. Efficacy of Targin in lowering BFI was demonstrated for these patients.

Safety

Both oxycodone and naloxone are registered with well-known safety profiles. The major safety concern was that naloxone could result in reduced analgesic efficacy of oxycodone or could precipitate withdrawal effects, particularly at high doses. This was not demonstrated.

The most frequent adverse effects affected the gastrointestinal system. Dizziness, nausea, headache, vomiting and diarrhoea were the most frequently reported events. Constipation was common but less frequent that with oxycodone. No deaths were considered drug-related in the clinical trials.

The postmarket study (OXN9002) enrolled 3353 patients. This study as well as data from 3 PSURs was included in the submission. No new safety signals of concern were identified from these data.

Risk-Benefit Analysis

The pharmacology studies have shown that there is some systemic effect from oral naloxone which is dose dependent. They also demonstrated an effect of naloxone when given with oxycodone in increasing the frequency of bowel movements in a dose-dependent manner. The effect on bowel movements was seen with doses of naloxone that were not associated with withdrawal effects in opioid-dependent individuals.

Food increased the mean C_{max} by 42% in study 1018 (a single dose study) but not in studies 1008 and 1009 where the increase was approximately 28%. Targin should be taken as in the pivotal clinical studies, that is, without regard to food.

Moderate to severe hepatic impairment increased the exposure to oxycodone up to 3 fold and to naloxone by 100 fold. For this reason the sponsor proposes Targin be contraindicated for these patients. Renal impairment also increased exposure to oxycodone, naloxone and the naloxone metabolite naloxone-3-glucuronide. Due to increases in exposure to both oxycodone and naloxone in elderly patients, particularly women, elderly patients should commence use of Targin at a low dose and if dose escalation is required this should be very cautious considering that at higher doses the effect of oxycodone may be reduced by the naloxone component of Targin.

Efficacy with respect to analgesic effect and improvement in measures of bowel function has been demonstrated for doses up to 80/ 40 mg daily, the maximum daily dose proposed by the sponsor. Limited evidence from study 3006 suggests the effect on bowel function is maintained at daily doses to 120/ 60 mg daily. No additional safety issues were apparent from the addition of oral

naloxone to oxycodone for patients with chronic non-malignant pain who had normal renal and hepatic function.

The Delegate proposed to approve Targin controlled release tablets containing oxycodone hydrochloride and naloxone hydrochloride dihydrate 5/ 2.5 mg, 10/ 5 mg, 20/ 10 mg and 40/ 20 mg for the management of moderate to severe chronic pain unresponsive to non-narcotic analgesia. The naloxone component in a fixed combination with oxycodone is indicated for the therapy and/ or prophylaxis of opioid-induced constipation.

The advice of the Advisory Committee on Prescription Medicines (ACPM) (which has succeeded ADEC) was requested on whether Targin should be indicated for use in children aged from 12 years, given that both oxycodone and naloxone have indications which include use in paediatric patients. No efficacy or safety data in children are available for the Targin formulation, however efficacy would not be expected to be substantially different in children aged from 12 years compared with adults.

The ACPM, having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, agreed with the Delegate's proposal.

ACPM recommended approval of the submission for the indication:

Management of moderate to severe chronic pain unresponsive to non-narcotic analgesia. The naloxone component in a fixed combination with oxycodone is indicated for the therapy and/ or prophylaxis of opioid-induced constipation

In making this recommendation, the Committee was satisfied that Targin demonstrated statistically and clinically meaningful improvements in bowel function as well as efficacy with respect to analgesic effect. Although no efficacy or safety data in children are available for the Targin formulation, efficacy would not be expected to be substantially different in children aged from 12 years compared with adults. Therefore, the Committee concurred with the Delegate that Targin should be indicated for use in children aged from 12 years as both oxycodone and naloxone have indications which include use in paediatric patients.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Targin controlled release tablets containing oxycodone hydrochloride and naloxone hydrochloride dihydrate 5/2.5mg, 10/5mg, 20/10mg and 40/20mg for the indication:

Management of moderate to severe chronic pain unresponsive to non-narcotic analgesia. The naloxone component in a fixed combination with oxycodone is indicated for the therapy and/or prophylaxis of opioid-induced constipation.

Attachment 1. Product Information

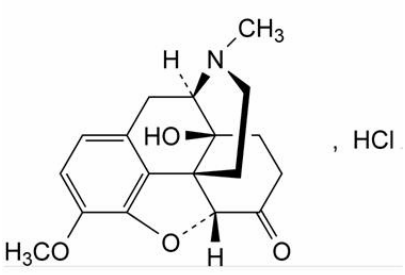
PRODUCT INFORMATION

TARGIN® tablets (5/2.5 mg, 10/5 mg, 20/10 mg, 40/20 mg)

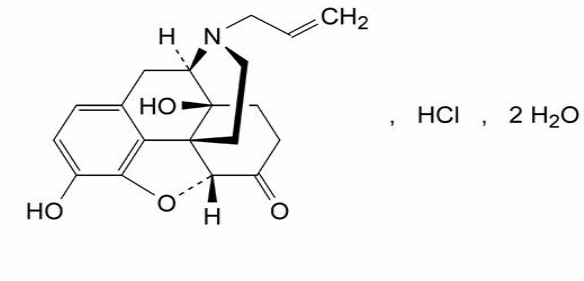
NAME OF DRUG Oxycodone hydrochloride and naloxone hydrochloride dihydrate.

DESCRIPTION

Oxycodone hydrochloride is a white, crystalline odourless powder readily soluble in water, sparingly soluble in ethanol and nearly insoluble in ether. The chemical name is 4,5α-epoxy-14-hydroxy-3-methoxy-17-methylmorphinan-6-one hydrochloride (CAS No: 124-90-3). The molecular formula is $C_{18}H_{21}NO_4$. HCl and molecular weight is 351.83. The pKa is 8.9 and the Partition Coefficient Log P is 0.7. The structural formula for oxycodone hydrochloride is:



Naloxone hydrochloride dihydrate is an off-white powder soluble in water. The chemical name is 17-allyl-4,5α-epoxy-3,14-dihydroxymorphinan-6-one hydrochloride dihydrate (CAS No: 51481-60-8). It is a synthetic congener of oxymorphone, with molecular formula $C_{19}H_{21}NO_4$. HCl.2(H_2O) and molecular weight 399.87. The pKa is 7.9 and the Partition Coefficient Log P is 1.5. The structural formula for naloxone hydrochloride dihydrate is:



The inactive ingredients in TARGIN® tablets are lactose, povidone, ethylcellulose, stearyl alcohol, talc and magnesium stearate. The tablets are coated with polyvinyl alcohol, titanium dioxide (E171), macrogol 3350 and talc. The tablet coat also contains brilliant blue CI42090 (5/2.5 mg tablets); iron oxide red CI77491 (20/10 mg tablets) and iron oxide yellow CI77492 (40/20 mg tablets).

PHARMACOLOGY

Actions

Oxycodone is a full opioid receptor agonist whose principal therapeutic action is analgesia. It has an affinity for endogenous mu, kappa and delta opiate receptors in the brain, spinal cord and peripheral organs (e.g. intestine). Binding of oxycodone to endogenous opioid receptors in the Central Nervous System (CNS) results in pain relief. Oxycodone is similar to morphine in its action. Other pharmacological actions of oxycodone are in the CNS (respiratory depression, antitussive, anxiolytic, sedative and miosis); smooth muscle (constipation, reduced gastric, biliary and pancreatic secretions, sphincter of Oddi spasm, and transient elevations in serum amylase); and cardiovascular system *via* histamine release and peripheral vasodilation (pruritus, flushing, red eyes, sweating and orthostatic hypotension).

Opioids may influence the hypothalamic-pituitary-adrenal or gonadal axes. Among the changes observed are an increase in serum prolactin and a decrease in levels of cortisol and testosterone. Clinical symptoms may accompany these hormonal changes.

Nonclinical studies have demonstrated differing immunomodulatory effects of naturally occurring opioids e.g. morphine, codeine. The clinical significance of these findings is not known. It is not known whether oxycodone, a semi-synthetic opioid, has similar effects.

Naloxone also has an affinity for endogenous opiate receptors in the brain, spinal cord and peripheral organs (e.g. intestine). However, in contrast to oxycodone, naloxone is a competitive opioid antagonist at opiate receptors, which can prevent or reverse the effects of opioid agonists.

Naloxone reduces bowel function disorders such as constipation that typically arise during opioid analgesic treatment with e.g. oxycodone, due to its local competitive antagonism of the opioid receptor-mediated oxycodone effect in the gut. Diarrhoea may be a possible effect of naloxone, especially at the beginning of treatment, and tends to be transient. Oral administration of naloxone is unlikely to result in a clinically relevant systemic effect due to a pronounced first-pass effect and its very low oral bioavailability upon oral administration (<3%).

The addition of naloxone at doses from 10 to 100 mg daily to methadone stabilised opioid addicts increases the frequency of bowel movements in a dose-dependent manner, with an effect seen starting from a naloxone dose of 20 mg daily. Oral naloxone also induced withdrawal symptoms in these methadone stabilised opioid addicts with a positive correlation between the methadone dose and the naloxone dose at which withdrawal occurred (p=0.02). Overall, the median dose of oral naloxone that induced clear symptoms of withdrawal appeared to be 70 mg daily. The onset of bowel movement and withdrawal was usually within the first 6 hours of naloxone administration.

Pharmacokinetics

The pharmacokinetic characteristics of oxycodone from TARGIN® tablets are comparable to those from controlled-release OxyContin® tablets, and demonstrate bioequivalence between these two long-acting oxycodone formulations. In addition, dose proportionality has been established for the TARGIN® 5/2.5 mg, 10/5 mg, 20/10 mg and 40/20 mg tablet strengths for both peak plasma concentrations (C_{max}) and extent of absorption (AUC) facilitating reliable dose titration and interchangeability between tablet strengths.

Absorption
Compared with morphine, which has an absolute bioavailability of approximately 30%, oxycodone has a high bioavailability of up to 87% following oral administration. Following absorption, oxycodone is distributed throughout the body. Approximately 45% is bound to plasma protein.

In a study of TARGIN® tablets in elderly subjects (≥ 65 years), plasma concentrations of oxycodone were only nominally affected by age, being approximately 18% greater in elderly compared to young subjects.

Female subjects have, on average, plasma oxycodone concentrations up to 25% higher than males on a bodyweight-adjusted basis.

Following ingestion of a high fat breakfast, the maximum plasma concentration (C_{max}) and bioavailability of oxycodone from TARGIN® tablets were nominally increased compared with fasting state administration, and not considered clinically relevant. TARGIN® tablets may be taken with or without food.

Following ingestion, oral naloxone is subject to a significant first-pass metabolism and its oral bioavailability is less than 3%.

Metabolism and Elimination
Oxycodone has an elimination half-life of approximately 3 hours and is metabolised principally in the liver *via* the cytochrome P450 enzyme system, to noroxycodone, oxymorphone, noroxymorphone, 6 α and β oxycodol and conjugated glucuronides. Oxymorphone and noroxymorphone have some analgesic activity. However, oxymorphone is present in plasma at low concentrations and noroxymorphone, due to its low lipophilicity, does not penetrate the blood-brain barrier to a significant extent. Consequently, the contribution of these metabolites to the overall analgesic effect is insignificant. Oxycodone and its metabolites are excreted in urine and faeces.

After parenteral administration, naloxone has a plasma half life of approximately one hour. Naloxone is metabolised in the liver to its principal metabolites naloxone glucuronide, 6 β-naloxol and its glucuronide and excreted in the urine.

Impaired hepatic function
A study has shown that plasma concentrations of both oxycodone and naloxone are elevated in patients with hepatic impairment. Naloxone plasma concentrations were affected to a greater extent than oxycodone. The clinical relevance of a relatively high naloxone exposure in hepatically impaired patients is not yet known. Caution must be exercised in administering TARGIN® tablets to patients with mild hepatic impairment. In patients with moderate to severe hepatic impairment, TARGIN® tablets are contraindicated.

Impaired renal function
A study has shown that plasma concentrations of both oxycodone and naloxone are elevated in patients with renal impairment. Naloxone plasma concentrations were affected to a greater extent than oxycodone. The clinical relevance of a relatively high naloxone exposure in renally impaired patients is not yet known. Caution should be exercised when administering TARGIN® tablets to patients with renal impairment (refer Special Risk Groups).

CLINICAL TRIALS:

1. Study 3001: this 12-week randomised, double-blind, parallel-group study, in patients with non-malignant pain experiencing opioid-induced constipation, assessed constipation symptoms (as measured by the Bowel Function Index [BFI]) in patients taking TARGIN® tablets compared with those taking oxycodone controlled release (CR) tablets. 272 patients were randomised to the double-blind phase (136 in each group), with the oxycodone dose between 20-50 mg/day. A secondary objective was to estimate the Average Pain over the last 24 hours (as measured by the Pain Intensity Scale) at each double-blind visit.

Patients in the TARGIN® tablet group showed an improved bowel function compared to those on oxycodone CR tablets from one week after the start of the double blind phase (Visit 4), continuing until the end of the study (Visit 8). Statistical significance was seen by 4 weeks/Visit 6 (15.2; $p<0.0001$; CI -18.2, -12.2). The mean pain intensity scores for Average Pain over the last 24 hours were comparable between the two groups, which was maintained until the end of the study with no significant treatment differences seen (0.014; 95% CI; -0.2026, 0.2304). The safety profile of TARGIN® tablets is consistent with those of other strong opioids.

2. Study 3006: this 12-week randomised, double-blind, parallel-group study, in patients with non-malignant pain experiencing opioid-induced constipation, also assessed constipation symptoms (measured by BFI) in patients taking TARGIN® tablets compared with those taking oxycodone CR tablets. 278 patients were randomised to the double-blind phase (130 on TARGIN® tablets, 135 on oxycodone CR tablets, 13 excluded because of study questionnaire irregularities), and the oxycodone dose for each group was between 60 and 80 mg/day.

Throughout the first 4 weeks of the double-blind phase (Visits 3-6), the difference between the mean BFI scores for the two groups was statistically significant in favour of TARGIN® tablets (-14.9; $p<0.0001$; CI -17.9, -11.9). The actual observed difference of the means was: -12.3 (TARGIN® tablets 40.94; oxycodone CR 53.27). Patients in the TARGIN® tablet group had a reduced mean observed BFI score from 1 week after randomisation into the double-blind phase (Visit 4), continuing to the end of the study (Visit 8), but this was not seen for the oxycodone CR tablet group. The mean pain intensity scores for Average Pain over the last 24 hours were comparable between the groups at baseline (Visit 3), and this was maintained through the double-blind phase until the end of the study (Visit 8), with no significant treatment differences seen between the two groups (model estimated treatment difference: 0.010; 95% CI; -0.14, 0.34). The safety profile of TARGIN® tablets is consistent with those of other strong opioids.

3. Study OXN1006 (impaired hepatic function): Significant differences in pharmacokinetic parameters between subjects with hepatic impairment (rated as mild, moderate or severe) and healthy volunteers were seen as summarised in the following table (values indicate % of healthy volunteer result):

	Mild (x% (90% CI))	Moderate (x% (90% CI))	Severe (x% (90% CI))
Oxycodone			
▪ AUC_{INF}	143% (111, 184)	319% (248, 411)	310% (241, 398)
▪ C_{max}	120% (99, 144)	201% (166, 242)	191% (158, 231)
▪ $t_{1/2Z}$	108% (70, 146)	176% (138, 215)	183% (145, 211)
Naloxone			
▪ AUCt	411% (152, 1112)	11518% (4259, 31149)	10666% (3944, 28847)
▪ C_{max}	193% (115, 324)	5292% (3148, 8896)	5252% (3124, 8830)
	$t_{1/2Z}$ and the corresponding AUC_{INF} of naloxone were not able to be calculated due to insufficient amount of data available. The bioavailability comparisons for naloxone were therefore based on AUCt values.		
Naloxone-3-glucuronide			
▪ AUC_{INF}	157% (89, 279)	128% (72, 227)	125% (71, 222)
▪ C_{max}	141% (100, 197)	118% (84, 166)	98% (70, 137)
▪ $t_{1/2Z}$	117% (72, 161)	77% (32, 121)	94% (49, 139)

4. Study OXN1007 (impaired renal function): Significant differences in pharmacokinetic parameters between subjects with renal impairment (rated as mild, moderate or severe) and healthy volunteers were seen as summarised in the following table (values indicate % of healthy volunteer result):

	Mild (x% (90% CI))	Moderate (x% (90% CI))	Severe (x% (90% CI))
Oxycodone			
▪ AUC_{INF}	153% (130, 182)	166% (140, 196)	224% (190, 266)
▪ C_{max}	110% (94, 129)	135% (115, 159)	167% (142, 196)
▪ $t_{1/2Z}$	149%	123%	142%
Naloxone			
▪ AUCt	2850% (369, 22042)	3910% (506, 30243)	7612% (984, 58871)
▪ C_{max}	1076% (154, 7502)	858% (123, 5981)	1675% (240, 11676)
	Due to insufficient amount of data available, $t_{1/2Z}$ and the corresponding AUC_{INF} of naloxone were not calculated. The bioavailability comparisons for naloxone were therefore based on AUCt values. The ratios may have been influenced by the inability to fully characterise the naloxone plasma profiles for healthy subjects.		
Naloxone-3-glucuronide			
▪ AUC_{INF}	220% (148, 327)	370% (249, 550)	525% (354, 781)
▪ C_{max}	148% (110, 197)	202% (151, 271)	239% (179, 320)
▪ $t_{1/2Z}$	No change	No change	No change

INDICATIONS

The management of moderate to severe chronic pain unresponsive to non-narcotic analgesia. The naloxone component in a fixed combination with oxycodone is indicated for the therapy and/or prophylaxis of opioid-induced constipation.

CONTRAINDICATIONS

Hypersensitivity to opioids, naloxone and any of the excipients or any situation where opioids are contraindicated, moderate to severe hepatic impairment, severe respiratory depression with hypoxia, elevated carbon dioxide levels in the blood, cor pulmonale, cardiac arrhythmias, uncontrolled bronchial asthma, severe chronic obstructive pulmonary disease, non-opioid induced paralytic ileus, pregnancy, lactation, severe CNS depression, increased cerebrospinal or intracranial pressure, brain tumour or head injury (due to the risk of increased intracranial pressure), uncontrolled convulsive disorders, suspected surgical abdomen, delayed gastric emptying, alcoholism, *delirium tremens,* concurrent administration of MAO-inhibitors and for 2 weeks after their cessation.

PRECAUTIONS

Respiratory depression:

Respiratory depression is the most important hazard of opioid preparations but occurs most frequently in overdose situations, in the elderly, in the debilitated, and in those suffering from conditions accompanied by hypoxia when even moderate doses may dangerously decrease respiration. TARGIN® tablets should be used with extreme caution in patients with a substantially decreased respiratory reserve or pre-existing respiratory depression and in patients with chronic obstructive pulmonary disease. Severe pain antagonises the respiratory depressant effects of opioids. However, should pain suddenly subside, these effects may rapidly become manifest.

Special Risk Groups:

As with all opioids, a reduction in dosage may be advisable in hypothyroidism. Exercise caution when administering TARGIN® tablets to elderly, infirm or debilitated patients, patients with mild hepatic impairment, patients with renal impairment, patients with severely impaired pulmonary function, opioid dependent patients. Precaution is required in hypotension, hypertension, hypovolaemia, diseases of the biliary tract (e.g. cholelithiasis), pancreatitis, inflammatory bowel disorders, prostatic hypertrophy, adrenocortical insufficiency (Addison's disease), toxic psychosis, myxoedema, opioid-induced paralytic ileus, pre-existing cardiovascular disease and in epileptic disorder or predisposition to convulsions.

As with all opioid preparations, patients who are to undergo cordotomy or other pain relieving surgical procedures should not receive TARGIN® tablets for 24 hours before surgery. Pain in the immediate pre-operative period, and any symptoms of opioid withdrawal, should be managed with short-acting analgesic agents. If further treatment with TARGIN® tablets is then indicated, the dosage should be adjusted to the new post-operative requirement.

TARGIN® tablets are not recommended for immediate pre-operative use and post-operative use for the first 24 hours after surgery. Depending on the type and extent of surgery, the anaesthetic procedure selected, other co-medication and the individual health status of the patient, the exact timing for initiating treatment with TARGIN® tablets depends on a careful risk-benefit assessment for each individual patient.

There is no clinical experience in patients with cancer associated with peritoneal carcinomatosis or with sub-occlusive syndrome in advanced stages of digestive and pelvic cancers. Therefore, the use of TARGIN® tablets in this population is not recommended.

Long-term opioid treatment:
In patients undergoing long-term opioid treatment with higher doses of opioids, the switch to TARGIN® tablets can initially provoke withdrawal symptoms or diarrhoea. These patients require specific attention.

Withdrawal symptoms:
TARGIN® tablets are not suitable for the treatment of withdrawal symptoms.

Use in chronic, non-cancer pain
The use of TARGIN® tablets for the treatment of chronic pain which is not due to cancer should be restricted to situations where:

- all other conservative methods of analgesia have been tried and have failed;
- the pain is having a significant impact on the patient's quality of life;
- there is no psychological contraindication, drug seeking behaviour or history of prescription medicine, illicit drug or alcohol misuse.

Opioids, where clinically indicated, are one component of, and should be integrated into, a comprehensive approach to chronic non-cancer pain. Appropriate patient selection is the key to successful treatment of moderate to severe pain with opioid analgesics.

An initial comprehensive assessment should be conducted using a biopsychosocial approach to identify a cause for the pain and the appropriateness of opioid therapy - and to identify psychosocial factors that may exacerbate pain or magnify overall distress (e.g.: depression, anxiety, post-traumatic stress disorder (PTSD), borderline personality disorder, marked family stressors, history of sexual abuse). In the absence of a clear indication for a strong opioid analgesic, drug-seeking behaviour must be suspected and resisted, particularly in individuals with a history of, or propensity for, drug abuse. Factors that may put the patient at increased risk of opioid abuse/addiction include a personal/family history of substance, prescription medication and alcohol abuse, and major psychosocial issues (e.g. psychological/psychiatric disorder). The use of opioids to treat predominant emotional distress should be avoided.

Generally, opioid analgesics are not initiated prior to a full initial clinical assessment and before consideration of other treatment options such as physiotherapy/exercise/rehabilitation approaches, psychosocial interventions such as CBT (cognitive-behavioural therapy) self-management approaches, and involvement of a psychologist or psychiatrist to address psychological co-morbidities which may be impacting on pain coping, and trials of other non-opioid pharmacotherapeutic or interventional strategies.

Prior to long term prescription, a trial of TARGIN® tablets or shorter acting opioid should be undertaken. Long term administration of TARGIN® tablets should only occur if this trial demonstrates that the pain is opioid sensitive. Opioid naïve patients who require rapid dose escalation with no concomitant pain relief within the trial period should generally be considered inappropriate for long term therapy.

One doctor only should be responsible for the prescription and monitoring of the patient's opioid use. Prescribers should consult appropriate clinical guidelines on the use of opioid analgesics in such patients (e.g. those published by the Australian Pain Society in the Medical Journal of Australia 1997; 167: 30-4).

Drug dependence

As with other opioids, tolerance and physical dependence tend to develop upon repeated administration of oxycodone. There is potential for abuse of the drug and for development of strong psychological dependence. TARGIN® tablets should therefore be prescribed and handled with a high degree of caution appropriate to the use of a drug with strong abuse potential.

Withdrawal symptoms may occur following abrupt discontinuation of all oxycodone therapy including TARGIN® tablets. Therefore, patients on prolonged therapy should be withdrawn gradually from the drug if it is no longer required for pain control.

Oxycodone should be used with caution and under close supervision in patients with pain not due to cancer who have a prior history of prescription medicine, alcohol or other substance abuse. However, in such cases, prior psychological assessment is essential and the prescribing doctor should consider whether the benefit of treatment outweighs the risk of abuse.

If abused parenterally or intranasally by individuals dependent on opioid agonists, such as heroin, morphine or methadone, TARGIN® tablets are expected to produce marked withdrawal symptoms due to the opioid receptor antagonist characteristics of naloxone, or to intensify already present withdrawal symptoms. Abuse by those drug addicts is strongly discouraged. Parenteral venous injection of the tablet constituents, especially talc, can be expected to result in local tissue necrosis, pulmonary granulomas and serious adverse reactions which may be fatal.

Formulation:

TARGIN® tablets must be swallowed whole and must not be broken, chewed or crushed, as this can lead to the rapid release of the active ingredients and absorption of a potentially fatal dose of oxycodone.

TARGIN® tablets consist of a dual-polymer matrix, intended for oral use only. TARGIN® tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption should not take TARGIN® tablets. The empty tablet matrix may be visible in the stool. TARGIN® tablets may produce positive results in sports agency drug testing procedures.

Renal and hepatic impairment

TARGIN® tablets should be used with caution in patients with mild hepatic impairment and patients with renal impairment (refer Pharmacokinetics). Whilst the administration of TARGIN® tablets to these patients does not result in significant levels of oxycodone active metabolites, the plasma concentrations in this patient population may be increased compared with patients having normal renal or hepatic function. Therefore, initiation of dosing in patients with mild hepatic impairment or patients with renal failure (CLcr < 60 mL/min) should be reduced to ⅓ to ½ of the usual dose with cautious titration and careful medical monitoring.

Because of the observed increase in naloxone plasma concentrations, and until the clinical relevance of this is established, TARGIN® tablets are contraindicated in patients with moderate to severe hepatic impairment.

Elderly
The plasma concentrations of oxycodone are only nominally affected by age, being approximately 18% greater in elderly as compared to young subjects. There were no differences in adverse event reporting between young and elderly subjects. The dosage should be adjusted to the intensity of the pain and the sensitivity of the individual patient.

Elderly, debilitated patients
As with other opioid initiation and titration, doses in elderly patients who are infirm or debilitated should be reduced to $^1/_3$ to ½ of the usual doses.

Use in children
TARGIN® tablets may be used in children from 12 years of age if clinically indicated, as both oxycodone and naloxone have been used in children.

Driving and operating dangerous machinery
TARGIN® tablets may impair the ability to drive and operate machinery, particularly at the commencement of treatment, after dosage increase or opioid rotation, and if TARGIN® tablets are combined with alcohol or other CNS depressants. The degree of driving impairment can depend upon the dosage and individual susceptibility, and some patients stabilised on a specific dosage may not be affected. All patients should consult with their physician and should not drive or operate machinery if their ability is impaired.

Carcinogenicity
Long-term studies in animals to evaluate the carcinogenic potential of oxycodone/naloxone in combination and oxycodone as a single entity have not been conducted. Naloxone was not carcinogenic in a 24-month dietary study in rats at doses up to 100 mg/kg/day, which is about 20-fold the naloxone dose at the maximal recommended clinical dose of TARGIN® tablets, on a body surface area basis.

Genotoxicity
The results of *in vitro* and *in vivo* studies indicate that the genotoxic risk of oxycodone to humans is minimal or absent at the systemic oxycodone concentrations that are achieved therapeutically. Oxycodone showed mutagenic activity in a mouse lymphoma assay, but was inactive in bacterial gene mutation assays. It also induced chromosomal aberrations in human lymphocytes *in vitro,* but not in immature erythrocytes *in vivo* in mice. Similar to oxycodone, naloxone induced gene mutations and chromosomal aberrations in mouse lymphoma cell lines and human lymphocytes *in vitro*, respectively, but did not induce chromosomal aberrations in immature erythrocytes under *in vivo* conditions.

Effects on Fertility
No studies have been conducted on the reproductive toxicity of the combination of oxycodone and naloxone. In reproductive toxicology studies of oxycodone alone, no evidence of impaired fertility was seen in male or female rats at oral oxycodone doses of 8 mg/kg/day, approximately the oxycodone dose at the maximal recommended clinical dose of TARGIN® tablets, on a body surface area basis. There were also no effects on the fertility in rats following oral administration of naloxone at doses up to 800 mg/kg/day, which is about 180-

fold the naloxone dose at the maximal recommended clinical dose of TARGIN® tablets, on a body surface area basis.

Use in pregnancy

Category C: TARGIN® tablets are contraindicated in pregnancy. Oxycodone and naloxone pass into the placenta. There are no adequate, and well controlled, studies on the use of TARGIN® tablets in pregnant women and during childbirth. In long-term administration during pregnancy, oxycodone may lead to withdrawal symptoms in the new-born child, and may cause respiratory depression during childbirth. Infants born to mothers who have received opioids during pregnancy should be monitored for respiratory depression.

No studies have been conducted on the reproduction toxicity of the combination of oxycodone and naloxone. There was no evidence of teratogenicity following oral administration of oxycodone during the period of organogenesis to rats at doses up to 7.2 mg/kg/day (approximately the oxycodone dose at the maximum recommended clinical dose of TARGIN® tablets, on a body surface area basis) or to rabbits at doses of up to 112 mg/kg/day (more than 20-fold the oxycodone dose at the maximal recommended clinical dose of TARGIN® tablets). There was also no evidence of teratogenicity following oral administration of naloxone during the period of organogenesis to rats and rabbits at respective doses up to 800 and 400 mg/kg/day, which is more than 160-fold the naloxone dose at the maximal recommended clinical dose of TARGIN® tablets on a body surface area basis. Because animal reproduction studies are not always predictive of human responses, this drug should not be used during pregnancy.

Use in lactation

TARGIN® tablets are contraindicated during lactation. Oxycodone passes into breast milk. A milk:plasma ratio of 3.4:1 was measured, and withdrawal symptoms can occur in breast-feeding infants when maternal administration of an opioid analgesic is stopped.

Oral administration of oxycodone to rats from early gestation to weaning did not affect postnatal development parameters at doses up to 6 mg/kg/day (about 0.7-fold the oxycodone dose at the maximal recommended clinical dose of TARGIN® tablets, on a body surface area basis). Oral administration of naloxone to rats from prior to mating to weaning, or from late gestation to weaning, did not affect reproductive or developmental indices up to 800 mg/kg/day (about 180-fold the naloxone dose at the maximal recommended clinical dose of TARGIN® tablets, on a body surface area basis).

It is not known if naloxone also passes into the breast milk. TARGIN® tablets should not be taken by breast-feeding mothers prior to the infant being weaned.

Interactions with other medicines

Anticholinergic agents

Concurrent use with oxycodone may result in an increased risk of severe constipation and/or urinary retention. The presence of naloxone in TARGIN® tablets, however, may serve to reverse the additive constipative effect, at least in part.

Antihypertensive agents

Hypotensive effects of these medications may be potentiated when used concurrently with oxycodone, leading to increased risk of orthostatic hypotension.

CNS depressants (including antidepressants, sedatives, hypnotics, general anaesthetics, phenothiazines, other tranquillisers, alcohol, other opioids, anti-histamines, anti-emetics and neuroleptic drugs, etc)

Concurrent use with oxycodone may enhance the CNS-depressant effect resulting in increased respiratory depression, hypotension, profound sedation or coma. Caution is recommended and the dosage of one or both agents should be reduced. Intake of alcoholic beverages while being treated with oxycodone should be avoided because this may lead to more frequent undesirable effects such as somnolence and respiratory depression. Oxycodone hydrochloride containing products should be avoided in patients exhibiting signs of alcohol, drug or medicines abuse or a history of any of these.

Coumarin derivatives

Opiate agonists have been reported to potentiate the anticoagulant activity of coumarin derivatives. Clinically relevant changes in International Normalised Ratio (INR or Quick-value) in both directions were observed when oxycodone and coumarin anticoagulants were co-administered.

Metoclopramide

Concurrent use with oxycodone may antagonise the effects of metoclopramide on gastrointestinal motility.

Monoamine Oxidase Inhibitors (MAOIs)

Non-selective MAOIs intensify the effects of opioid drugs which can cause anxiety, confusion and significant respiratory depression. Severe and sometimes fatal reactions have occurred in patients concurrently administered MAOIs and pethidine. Oxycodone should not be given to patients taking non-selective MAOIs or within 14 days of stopping such treatment. As it is unknown whether there is an interaction between selective MAOIs (e.g. selegiline) and oxycodone, caution is advised with this drug combination.

Neuromuscular blocking agents

Oxycodone may enhance the effects of neuromuscular blocking agents resulting in increased respiratory depression.

Opioid agonist analgesics (including morphine, pethidine)

Additive CNS depressant, respiratory depressant and hypotensive effects may occur if two or more opioid agonist analgesics are used concurrently.

Opioid agonist-antagonist analgesics (including pentazocine, butorphanol, buprenorphine)
Mixed agonist/antagonist analgesics may reduce the analgesic effect of oxycodone and/or may precipitate withdrawal symptoms.

CYP2D6 AND CYP3A4 inhibitors and inducers
Oxycodone is metabolized in part via the CYP2D6 and CYP3A4 pathways. The activities of these metabolic pathways may be inhibited or induced by various co-administered drugs, which may alter plasma oxycodone concentrations. Oxycodone doses may need to be adjusted accordingly. Quinidine, a potent CYP2D6 inhibitor, has blocked the formation of oxymorphone, while the oxycodone concentration increased marginally. Concurrent administration of quinidine does not alter the pharmacodynamic effects of oxycodone. Ketoconazole, a CYP3A4 inhibitor, inhibited the formation of noroxycodone from oxycodone in human liver microsomes *in vitro*. Oxycodone metabolism may be blocked by a variety of drugs (e.g. cimetidine, certain cardiovascular drugs and antidepressants), although such blockade has not yet been shown to be of clinical significance with TARGIN® tablets.

In vitro metabolic studies indicate that no clinically relevant interactions are to be expected between oxycodone and naloxone. At therapeutic concentrations, TARGIN® tablets are not expected to cause clinically relevant interactions with other concomitantly administered drugs metabolised over the CYP isomers, CYP1A2, CYP2A6, CYP2C9/19, CYP2D6, CYP2E1 and CYP3A4. In addition, the likelihood of clinically relevant interactions between paracetamol, acetylsalicylic acid or naltrexone and the combination of oxycodone and naloxone in therapeutic concentrations is minimal.

Alcohol
Dissolution studies with TARGIN ® tablets were conducted Standard Gastric Fluid sine pepsin (SGFsp) dissolution media, modified with ethanol at concentrations up to 40%v/v, representative of the most extreme conditions likely to be encountered *in vivo*. The prolonged-release characteristics of TARGIN® tablets were maintained under these test conditions, and no breakdown of the controlled release mechanism of the formulation was observed.

ADVERSE EFFECTS
Adverse drug reactions are typical of full opioid agonists, and tend to reduce with time. The naloxone in TARGIN® tablets reduces bowel function disorders such as constipation that typically arise during oxycodone analgesic treatment. Anticipation of adverse drug reactions and appropriate patient management can improve acceptability. The following adverse events were reported in the pivotal trials, during the double-blind phase, without attributing causality.

The incidence of adverse events for TARGIN® tablets and active comparator reported in ≥ 1% of subjects by system organ class ≥ 10% and preferred term in the double-blind phase of pivotal clinical study **OXN3001**:

Adverse Events in Study OXN3001:	**TARGIN® tablet dose:** Equivalent to OxyContin® tablets (N=162)	(%)	**Active Comparator:** OxyContin® tablets 20-50 mg/day (N=160)	(%)
Gastrointestinal disorders				
Dyspepsia	1	(0.6%)	4	(2.5%)
Diarrhoea	9	(5.6%)	11	(6.8%)
Constipation	1	(0.6%)	8	(4.9%)
Abdominal pain	2	(1.3%)	7	(4.3%)
Abdominal pain upper	2	(1.3%)	2	(1.2%)
Nausea	10	(6.3%)	17	(10.5%)
Vomiting	2	(1.3%)	7	(4.3%)
Infections & infestations				
Urinary Tract Infection	9	(5.6%)	4	(2.5%)
Bronchitis	3	(1.9%)	1	(0.6%)
Cystitis	0	(0.0%)	4	(2.5%)
Nasopharyngitis	4	(2.5%)	8	(4.9%)
Lower Respiratory Tract Infection	3	(1.9%)	3	(1.9%)
Gastroenteritis	3	(1.9%)	3	(1.9%)
Musculoskeletal & connective tissue disorders				
Neck pain	2	(1.3%)	3	(1.9%)
Myalgia	3	(1.9%)	2	(1.2%)
Back pain	7	(4.4%)	5	(3.1%)
Arthralgia	4	(2.5%)	5	(3.1%)
Nervous system disorders				
Dizziness	5	(3.1%)	9	(5.6%)
Headache	5	(3.1%)	6	(3.7%)
Tremor	2	(1.3%)	3	(1.9%)

Incidence of adverse events for TARGIN® tablets and active comparator reported in ≥ 1% of subjects by system organ class (≥10 %) and preferred term in the double-blind phase of pivotal clinical study **OXN3006**:

Adverse Events in Study OXN3006:	**TARGIN® tablet dose:** Equivalent to OxyContin® tablets (N=130)	(%)	**Active Comparator:** OxyContin® tablets 60-80 mg/day (N=135)	(%)
Gastrointestinal disorders				
Abdominal pain	10	(7.7%)	2	(1.5%)
Abdominal pain upper	4	(3.1%)	3	(2.2%)
Constipation	1	(0.8%)	2	(1.5%)
Diarrhoea	6	(4.6%)	4	(3.0%)
Dry mouth	1	(0.8%)	2	(1.5%)
Nausea	13	(10.0%)	9	(6.7%)
Vomiting	4	(3.1%)	1	(0.7%)
General disorders & admin. site conditions				
Chest pain	2	(1.5%)	1	(0.7%)
Chills	3	(2.3%)	2	(1.5%)
Drug withdrawal syndrome	0	(7.7%)	4	(3.0%)
Fatigue	2	(1.5%)	4	(3.0%)
Feeling cold	3	(2.3%)	0	(0.0%)
Pain	10	(7.7%)	5	(3.7%)
Infections & infestations				
Gastroenteritis	2	(1.5%)	4	(3.0%)
Influenza	1	(0.8%)	4	(3.0%)
Nasopharyngitus	1	(0.8%)	3	(2.2%)
Sinusitis	2	(1.5%)	2	(1.5%)
Urinary Tract Infection	4	(3.1%)	2	(1.5%)
Musculoskeletal & connective tissue disorders				
Arthralgia	2	(1.5%)	1	(0.7%)
Back pain	5	(3.8%)	5	(3.7%)
Osteoarthritis	1	(0.8%)	3	(2.2%)
Nervous system disorders				
Dizziness	1	(0.8%)	2	(1.5%)
Headache	7	(5.4%)	5	(3.7%)
Sciatica	5	(3.8%)	0	(0.0%)

Incidence of adverse events for TARGIN® tablets, active comparator and placebo reported in ≥ 2% of subjects by system organ class (≥10 %) and preferred term in the double-blind phase of pivotal clinical study **OXN3401**:

Adverse Events in Study OXN3401:	**TARGIN® tablet dose:** Equivalent to OxyContin® tablets (N=154)	(%)	**Active Comparator:** OxyContin® tablets 20-40 mg/day (N=151)	(%)	**Placebo (N=158) N (%)**
Ear & labyrinth disorders					
Vertigo	2	(1.3%)	5	(3.3%)	5 (3.2%)
Gastrointestinal disorders					
Constipation	13	(8.4%)	18	(11.9%)	8 (5.1%)
Diarrhoea	8	(5.2%)	4	(2.6%)	7 (4.4%)
Dyspepsia	3	(1.9%)	7	(4.6%)	3 (1.9%)
Nausea	10	(6.5%)	12	(7.9%)	11 (7.0%)
Vomiting	8	(5.2%)	7	(4.6%)	5 (3.2%)
General disorders & admin. site conditions					
Fatigue	4	(2.6%)	8	(5.3%)	4 (2.5%)
Infections and infestations					
Nasopharyngitis	2	(1.3%)	5	(3.3%)	4 (2.5%)
Investigations					
Blood triglycerides increased	3	(1.9%)	5	(3.3%)	3 (1.9%)
Nervous system disorders					
Dizziness	2	(1.3%)	9	(6.0%)	6 (3.8%)
Headache	5	(3.2%)	6	(4.0%)	11 (7.0%)
Skin & subcutaneous tissue disorders					
Hyperhidrosis	5	(3.2%)	2	(1.3%)	7 (4.4%)
Pruritus	5	(3.2%)	3	(2.0%)	4 (2.5%)

Adverse drug reactions attributable to TARGIN® tablets were reported at the frequencies below:
Very common: ≥ 10%
Common: ≥ 1% and < 10%;
Uncommon: ≥ 0.1% and < 1%;
Rare: ≥ 0.01% and < 0.1%;
Very rare: < 0.01%, or not known (cannot be estimated from the available data)

Cardiac disorders
Uncommon palpitations (in the context of withdrawal symptoms)

Ear and labyrinth disorders
Common vertigo

Eye disorders
Uncommon visual disturbances

Gastrointestinal disorders
Common abdominal pain, constipation, diarrhoea, dry mouth, dyspepsia, nausea, vomiting
Uncommon eructation, flatulence,

General disorders and application site conditions
Common asthenic conditions, chills
Uncommon chest pain, drug withdrawal syndrome, malaise, peripheral oedema

Hepatobiliary disorders
Common hepatic enzymes increased

Immune system disorders
Uncommon hypersensitivity

Injury, poisoning and procedural complications
Uncommon injuries from accidents

Metabolic and nutrition disorders
Common anorexia

Musculoskeletal and connective tissue disorders
Common muscle spasms, muscle twitching, myalgia

Nervous system disorders
Common dizziness, headache
Uncommon disturbance in attention, paraesthesia, somnolence, speech disorder, tremor
Rare convulsions (particularly in persons with epileptic disorder or predisposition to convulsions), sedation, syncope

Psychiatric disorders
Uncommon anxiety, confusional state, depression, euphoria, hallucinations, insomnia, nervousness, restlessness, thinking abnormal
Rare nightmares

Renal and urinary disorders
Uncommon micturition urgency
Rare urinary retention

Reproduction system and breast disorders
Uncommon erectile dysfunction

Respiratory, thoracic and mediastinal disorders
Uncommon dyspnoea
Not known respiratory depression

Skin and subcutaneous tissue disorders
Common hyperhidrosis, pruritus, rash

Vascular disorders
Common decrease in blood pressure
Uncommon increase in blood pressure

The following additional adverse events are known for **oxycodone**:
Due to its pharmacological properties, oxycodone may cause respiratory depression, miosis, bronchial spasm, and spasms of non-striated muscles as well as suppress the cough reflex.

Cardiac disorders
Uncommon bradycardia, ST depression, supraventricular tachycardia

Ear and labyrinth disorders
Uncommon tinnitus

Eye disorders
Uncommon miosis

Gastrointestinal disorders
Common gastritis, hiccup
Uncommon colic, dental caries, dysphagia, gastrointestinal disorder, hiccup, stomatitis
Not known ileus

General disorders and administration site conditions
Common drug withdrawal syndrome, fever
Uncommon facial flushing, lymphoadenopathy, neck pain, oedema
Rare drug tolerance, thirst

Hepatobiliary disorders
Uncommon biliary spasm, cholestasis

Immune system disorders
Uncommon allergic reaction, anaphylactoid reaction
Very rare anaphylactic reaction

Metabolic and nutrition disorders
Uncommon hyponatraemia, increased appetite
Rare dehydration

Musculoskeletal and connective tissue disorders
Uncommon muscle contractions involuntary, muscular rigidity

Nervous system disorders
Common faintness
Uncommon amnesia, drowsiness, gait abnormal, hyperkinesia, hypertonia, hypoaesthesia, hypothermia, raised intracranial pressure, stupor, taste perversion

Psychiatric disorders

Common	agitation, mood changes
Uncommon	affect lability, disorientation, dysphoria, libido decreased
Not known	drug dependence

Renal and urinary disorders

Common	ureteric spasm, urinary abnormalities, urinary tract infection

Reproductive system and breast disorders

Rare	amenorrhoea

Respiratory, thoracic and mediastinal disorders

Common	bronchospasm, pharyngitis, voice alteration

Skin and subcutaneous tissue disorders

Uncommon	exfoliative dermatitis
Rare	dry skin
Very rare	urticaria

Vascular disorders

Common	orthostatic hypotension
Uncommon	migraine, vasodilatation

If nausea and vomiting are troublesome, oxycodone may be combined with an antiemetic. Constipation must be treated with appropriate laxatives. Overdose may produce respiratory depression. Compared with other opioids, oxycodone is associated with low histamine release although urticaria and pruritus may occur.

Summary of Post-marketing data:

Post-marketing data are available from three Periodic Safety Update Reports (PSURs) for the period 31 March 2006 to 30 September 2007. Overall, 95 case reports were received from 5 countries, of which 66 were initial reports. A total of 205 adverse events were reported from the 95 cases, the majority being nervous system orders (N=37), gastrointestinal disorders (N=32), psychiatric disorders (N=30), and general disorders and administration site conditions (N=29). Of the 95 cases, 39 were rated as serious unlisted adverse events.

DOSAGE AND ADMINISTRATION

TARGIN® tablets are to be swallowed whole and are not to be broken, chewed or crushed. Taking broken, chewed or crushed tablets could lead to the rapid release and absorption of a potentially toxic dose of oxycodone that could be fatal.

TARGIN® tablets are intended for oral use only. The required dosage should be taken with sufficient liquid, with or without food, at 12-hourly intervals (e.g. 8 am and 8 pm). The analgesic efficacy of TARGIN® tablets is equivalent to OxyContin® tablets.

The dosage for an individual patient is dependent upon the severity of the pain, functional status, sensitivity (side effects) and the patient's previous history of analgesic requirements, including opioid analgesics.

Adults and children from 12 years of age:
Prior to initiation and titration of doses, refer to the **PRECAUTIONS** section for information on Special Risk Groups.

The usual starting dose for opioid-naïve patients or patients presenting with moderate to severe chronic pain uncontrolled by weaker opioids is one TARGIN® tablet 10/5 mg at 12-hourly intervals, or one TARGIN® tablet 5/2.5 mg 12-hourly for patients with mild hepatic impairment and patients with renal impairment. The dose should then be cautiously titrated, as frequently as every 1-2 days, if necessary, to achieve pain relief.

Patients already being treated with opioids may be started on higher doses of TARGIN® tablets, depending upon their previous opioid exposure.

Patients receiving oral morphine prior to treatment with TARGIN® tablets should have their daily dose of TARGIN® tablets established based on the following ratio: 10 mg of oral oxycodone is equivalent to 20 mg of oral morphine. It is emphasised that this is a guide to the required dose of TARGIN® tablets only. Inter-patient variability in sensitivity and response to opioid analgesics requires that each patient is carefully titrated to the appropriate dose.

Patients receiving other oral oxycodone formulations may be transferred to TARGIN® tablets at the same total daily dosage, equally divided into two 12-hourly TARGIN® tablets doses.

Increasing severity of pain may require an increased dosage of TARGIN® tablets using the 5/2.5 mg, or where appropriate, 10/5 mg tablet strengths, either alone or in combination, to achieve a stable dose providing adequate pain relief. The correct dosage for any individual patient is the minimum dose that controls the pain, provides functional improvement and is well tolerated, for a full 12 hours. Patients should be titrated to pain relief and functional improvement unless unmanageable adverse drug reactions prevent this.

Some patients taking TARGIN® tablets according to a regular time schedule may require immediate release analgesics (e.g. immediate release oxycodone) as "rescue" medication for breakthrough pain. TARGIN® tablets are a prolonged release formulation and are not intended to treat breakthrough pain. Should breakthrough pain treatment be necessary, it is generally recommended that a single dose of rescue medication should be approximately 1/6 to 1/12 of the equivalent daily dose of oxycodone hydrochloride. The need for more than two doses of "rescue" medication per day is usually an indication for the patient to be re-assessed and, if appropriate, the dosage of TARGIN® tablets increased.

Due to the limited exposure of patients receiving daily doses beyond 80/40 mg, the maximum recommended daily dose of TARGIN® tablets is 80/40 mg (corresponding to 12-hourly administration of TARGIN® tablets 40/20 mg). Patients requiring higher dosages should be administered supplemental, single entity controlled release oxycodone at the same time intervals. In the case of supplemental oxycodone dosing, the beneficial effect of naloxone on bowel function may be impaired. After complete discontinuation with TARGIN® tablets and a subsequent switch to another opioid, a worsening of bowel function can be expected.

Moderate to severe pain in the majority of patients is well managed by the symmetric administration (identical morning and evening doses) of TARGIN® tablets at the established, stable 12-hourly fixed dosage schedule. However, some patients may benefit from an asymmetric dosing schedule (higher dose in the morning or evening) tailored to their analgesic needs, depending upon the nature of their variable, diurnal pain severity. In these patients, the lowest total daily analgesic dose that provides adequate pain relief should always still be prescribed.

TARGIN® tablets should not be prescribed and taken by the patient for longer than absolutely necessary to manage their pain. If long-term pain treatment is anticipated given the nature and severity of the illness careful, and regular assessment and monitoring is required to establish the clinical need for ongoing treatment with opioid analgesic. When opioid treatment is no longer needed, the dose should be gradually reduced to minimise symptoms of withdrawal.

Controlled pharmacokinetic studies in elderly patients (aged over 65 years) have shown that compared with younger adults the clearance of oxycodone is only slightly reduced. No untoward adverse drug reactions were seen based on age, therefore adult doses and dosage intervals are appropriate in this patient population.

Non-Cancer Pain
Daily doses of up to 40/20 mg TARGIN® tablets are usually sufficient for the treatment of moderate to severe, chronic non-cancer pain, but higher doses may be required.

Use in children: Not recommended for use in children below 12 years of age.

OVERDOSAGE
Depending upon the history of the patient, an overdose of TARGIN® tablets may be manifested by symptoms triggered by oxycodone (opioid receptor agonist) or by naloxone (opioid receptor antagonist). However, symptoms of naloxone overdosage are unlikely (treat symptomatically in a closely-supervised environment).

Symptoms of oxycodone overdosage: miosis (dilated if hypoxia is severe), cold and/or clammy skin, respiratory depression (reduced respiratory rate and/or tidal volume, cyanosis), extreme somnolence progressing to stupor or coma, skeletal muscle flaccidity, bradycardia and hypotension. Coma, non-cardiogenic pulmonary oedema and circulatory failure may occur in more serious cases, and may lead to a fatal outcome.
The features of overdosage may be delayed with a controlled release product such as TARGIN® tablets.

Treatment of oxycodone overdosage: Primary attention should be given to immediate supportive therapy with the establishment of adequate respiratory exchange through the provision of a patent airway and institution of assisted or controlled ventilation. Adequate body temperature and fluid balance should be maintained.

Oxygen, intravenous fluids, vasopressors, infusions and other supportive measures should be employed, as necessary, to manage the circulatory shock accompanying an overdose. Cardiac arrest or arrhythmias may require cardiac massage or defibrillation. Artificial ventilation should be applied if necessary and fluid and electrolyte metabolism maintained.

Activated charcoal may reduce absorption of the drug if given within one to two hours after ingestion. Administration of activated charcoal should be restricted to patients who are fully conscious with an intact gag reflex or protected airway. A saline cathartic or sorbitol added to the first dose of activated charcoal may speed gastrointestinal passage of the product. In patients who are not fully conscious or have an impaired gag reflex, consideration should be given to administering activated charcoal via a nasogastric tube, once the airway is protected.

Whole bowel irrigation (eg 1 or 2 litres of polyethylene glycol solution orally per hour until rectal effluent is clear) may be useful for gut decontamination. Whole bowel irrigation is contraindicated in patients with bowel obstruction, perforation, ileus, haemodynamic instability or compromised, unprotected airways and should be used cautiously in debilitated patients and where the condition may be further compromised. Concurrent administration of activated charcoal and whole bowel irrigation may decrease the effectiveness of the charcoal (there may be competition for the charcoal binding site between the polyethylene glycol and the ingested drugs) but the clinical relevance is uncertain. Prolonged periods of observation (days) may be required for patients who have overdosed with long-acting preparations.

If there are signs of clinically significant respiratory or cardiovascular depression, an opioid antagonist should be considered. Naloxone hydrochloride at a dose of 0.4-2 mg intravenously is a specific antidote for respiratory depression due to overdosage or as a result of unusual sensitivity to oxycodone. Concomitant efforts at respiratory resuscitation should be carried out. Administration of naloxone should be repeated at 2-3 minute intervals, as clinically necessary. An infusion of 2 mg naloxone in 500 mL of 0.9% sodium chloride or 5% dextrose (0.004 mg/mL naloxone), run at a rate aligned to previously administered bolus doses and to the patient's response, is also a possible alternative. In this case, the infusion should be run at a rate consistent with the previously administered bolus doses and to the patient's response.

The duration of action of oxycodone may exceed that of the antagonist. Consequently, the patient should remain under continued surveillance and dosing of the antagonist continued as needed to maintain adequate respiration.

In an individual physically dependent on opioids, administering opioid antagonists may precipitate a withdrawal syndrome and should be avoided if possible. Withdrawal syndrome may lead to agitation, hypertension, tachycardia and risk of vomiting with possible aspiration. The severity of withdrawal depends on the degree of dependence and the antagonist dose. If required for serious respiratory depression, the antagonist should be administered with extreme care, commencing with 10 to 20% of the usual recommended initial dose and titrating.

Toxicity: Due to the great interindividual variation in sensitivity to opioids it is difficult to determine an exact dose of any opioid that is toxic or lethal. Crushing and taking the contents of a controlled release dosage form leads to the release of oxycodone in an immediate fashion; this might result in a fatal overdose. The toxic effects and signs of overdosage may be less pronounced than expected, when pain and/or tolerance are manifest.

Please phone the Poisons Information Centre on 131126 for advice on managing overdose.

PRESENTATIONS AND STORAGE CONDITIONS

TARGIN® tablets are available as oblong, unscored film-coated tablets in blister pack size of 20 tablets as follows:

- 5 mg anhydrous oxycodone hydrochloride/2.5 mg anhydrous naloxone hydrochloride (as the dihydrate) (light blue, marked "OXN" on one side and "5" on other)
- 10 mg anhydrous oxycodone hydrochloride /5 mg anhydrous naloxone hydrochloride (as the dihydrate) (white, marked "OXN" on one side and "10" on other);
- 20 mg anhydrous oxycodone hydrochloride /10 mg anhydrous naloxone hydrochloride (as the dihydrate) (pink, marked "OXN" on one side and "20" on other);
- 40 mg anhydrous oxycodone hydrochloride /20 mg anhydrous naloxone hydrochloride (as the dihydrate) (yellow, marked "OXN" on one side and "40" on other).

Store below 25ºC.

POISON SCHEDULE: S8

NAME AND ADDRESS OF SPONSOR

Mundipharma Pty Limited
ABN 87 081 322 509
50 Bridge Street
SYDNEY NSW 2000

DATE OF APPROVAL

5 March 2010.

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