LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Oxycodone/Naloxone Nordic Drugs (naloxone, oxycodone hydrochloride, naloxone hydrochloride dihydrate, oxycodone, naloxone hydrochloride, anhydrous)

Asp no: 2022-0969

This module reflects the scientific discussion for the approval of Oxycodone/Naloxone Nordic Drugs. The procedure was finalised on 2025-04-02. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, a marketing authorisation has been granted for Oxycodone/Naloxone Nordic Drugs, 40 mg/20 mg, Prolonged-release tablet.

The active substance is naloxone, oxycodone hydrochloride, naloxone hydrochloride dihydrate, oxycodone, naloxone hydrochloride, anhydrous. A comprehensive description of the indication and posology is given in the SmPC.

For recommendations to the marketing authorisation not falling under Article 21a/22a/22 of Directive 2001/83/EC and conditions to the marketing authorisation pursuant to Article 21a/22a/ 22 of Directive 2001/83/EC to the marketing authorisation, please see section VI.

The application for Oxycodone/Naloxone Nordic Drugs, 5 mg/2,5 mg, 10 mg/5 mg, 20 mg/10 mg, 30 mg/15 mg, 40 mg/20 mg, Prolonged-release tablet, is a generic application submitted according to Article 10(1) of Directive 2001/83/EC. The applicant applies for a marketing authorisation in Sweden through a National Procedure.

The reference medicinal product chosen for the purposes of establishing the expiry of the data protection period is Targin, 10/5 mg, prolonged-release tablet, authorised in DE since 2006, with Mundipharma as marketing authorisation holder.

Potential similarity with orphan medicinal products
N/A

II. QUALITY ASPECTS

II.1 Drug Substance

The structure of the drug substance has been adequately proven and its physico-chemical properties are sufficiently described.

The manufacture of the drug substance has been adequately described and satisfactory specifications have been provided for starting materials, reagents and solvents.

The drug substance specification includes relevant tests and the limits for impurities and degradation products have been justified. The analytical methods applied are suitably described and validated.

Stability studies confirm the retest period.

II.2 Medicinal Product

The medicinal product is formulated using excipients listed in section 6.1 in the Summary of Product Characteristics.

The manufacturing process has been sufficiently described and critical steps identified.

The tests and limits in the specification are considered appropriate to control the quality of the finished product in relation to its intended purpose.

Stability studies have been performed and data presented support the shelf life and special precautions for storage claimed in the Summary of Product Characteristics, sections 6.3 and 6.4.

III. NON-CLINICAL ASPECTS

Pharmacology/Pharmacokinetics/Toxicology
Pharmacodynamic, pharmacokinetic and toxicological properties of oxycodone/naloxone are well known. As oxycodone/naloxone is a widely used, well-known active substance, no further studies are required and the applicant provides none. Overview based on literature review is, thus, appropriate.

Environmental Risk Assessment (ERA)
Since Oxycodone/Naloxone Nordic Drugs is a generic product, it will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

There are no objections to approval of Oxycodone/Naloxone Nordic Drugs from a non-clinical point of view.

IV. CLINICAL ASPECTS

Pharmacokinetics
In support of the application, the Applicant has submitted five bioequivalence studies, comparing the Oxycodone/Naloxone prolonged release tablets and Targin Retardtabletten. Additionally, one dose proportionality study across the entire dose range, i.e. from 5/2.5 mg to 40/20 mg, has been performed.

Pharmacokinetic properties of the active substances

Absorption: Following oral administration, oxycodone has a high absolute bioavailability of up to 87 % whereas naloxone has a very low systemic availability (< 3 %). There are no restrictions with respect to food in the SmPC of the originator.

Linearity: Following administration of oxycodone prolonged-release tablets, linear pharmacokinetics have been demonstrated within the dose range 10-80 mg.

Elimination: The terminal half-life of oxycodone is approximately 4-5 hours. After parenteral administration, the plasma half-life of naloxone is approximately 1 hour.

Pharmacokinetic studies

The following bioequivalence studies have been conducted:

Study 502B13

- Comparative bioavailability study of oxycodone and naloxone after **single dose** administration (**fasting** conditions) of Oxycodone HCl 5 mg/Naloxone HCl 2.5 mg PR Tablets and Targin 5 mg/2.5 mg Retardtabletten (Mundipharma) in healthy subjects

Study 503B13

- Comparative bioavailability study of oxycodone and naloxone after **single dose** administration (**fed** conditions) of Oxycodone HCl 5 mg/Naloxone HCl 2.5 mg PR Tablets and Targin 5 mg/2.5 mg Retardtabletten (Mundipharma) in healthy subjects

Study 347B13

- Comparative bioavailability study of oxycodone and naloxone after **single dose** administration (**fasting** conditions) of Oxycodone HCl 40mg/Naloxone HCl 20mg PR Tablets and Targin 40 mg/20 mg Retardtabletten (Mundipharma) in healthy subjects

Study 348B13

- Comparative bioavailability study of oxycodone and naloxone after **single dose** administration (**fed** conditions) of Oxycodone HCl 40 mg/Naloxone HCl 20 mgPR Tablets and Targin 40 mg/20 mg Retardtabletten (Mundipharma) in healthy subjects

Study 520B13

- Comparative bioavailability study of oxycodone and naloxone after **multiple dose** administration (fasting conditions) of Oxycodone HCl 20 mg/Naloxone HCl 10 mg PR Tablets and Targin® 20 mg/10 mg Retardtabletten (Mundipharma) in healthy subjects

Study 021B14

- **Dose proportionality** study of oxycodone and naloxone after single dose administration (fasting conditions) of all proposed tablet strengths (i.e. 40/20 mg, 30/15 mg, 20/10 mg, 10/5 mg and 5/2.5 mg in 30 healthy subjects

Blood samples were collected pre-dose (within 60 min before IP administration) and up to 36 hrs after drug administration in the single dose studies (including the dose-proportionality study) as well as on day 4 (PK day) of the multiple dose study. Plasma concentrations of oxycodone, naloxone and the stable metabolite naloxone-3-glucuronide were determined with validated LC-MS/MS methods, and statistical analysis was performed on log-transformed pharmacokinetic variables using ANOVA. Of note, since naloxone is hardly quantifiable in plasma, statistical analysis of this analyte is not considered reliable; therefore, naloxone-3-glucoronide was used as surrogate analyte for naloxone.

In the single dose studies, the 90% confidence interval for the AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} ratios of the test and reference products fell within the conventional acceptance range of 80.00-125.00%. In the multiple-dose study, the 90% confidence interval for the $AUC_{(0-\tau)ss}$, $C_{max,ss}$ and $C_{\tau,ss}$ ratios of the test and reference products fell within the conventional acceptance range of 80.00-125.00%. Moreover, in the dose-proportionality study, for all tablet strengths the dose adjusted arithmetic mean C_{max}, $AUC_{(0-t)}$ and $AUC_{(0-\infty)}$ of both oxycodone and naloxone-3-glucuronide were consistently within ± 25% as compared to the corresponding arithmetic means for the lowest tablet strength (i.e. 5/2.5 mg).

Discussion and overall conclusion

The bioequivalence studies and their statistical evaluations were in accordance with accepted standards for bioequivalence testing, as stated in the Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1/Corr). The bioanalytical methods were adequately validated.

The applied product is a single unit formulation, where the different applied strengths do not fulfil the requirement of pharmaceutical proportionality. The reference SmPC recommends intake irrespective of food. For such formulations the Guideline on the pharmacokinetics and clinical evaluation of modified release dosage forms (EMA/CHMP/EWP/280/96 Rev1) requests single dose BE studies under *fasting* conditions for *each strength* of the product, whereas in the *fed* state single dose BE studies should be performed at *two strengths* representing the most extreme differences for the whole set of strengths.

The strengths 5/2.5 mg and 40/20 mg can be considered as relevant extremes for the whole set of strengths. Consequently, from a pharmacokinetic perspective, single dose studies of the strengths 5/2.5 mg and 40/20 mg respectively, in both fasted and fed conditions, are considered adequate and sufficient.

One multiple dose BE study may be sufficient and predictive for the whole series of strengths, provided that single dose data in fasted state indicate that the different strengths of test formulations exhibit comparable release characteristics. This has been adequately shown in the dose-proportionality study. Also, it is considered acceptable to perform the multiple dose study with the 20/10 mg tablet strength (instead of the highest strength) for safety/ethical reasons.

In conclusion: Since all study results comply with the conventional acceptance limits of bioequivalence and since the bracketing approach (strength biowaiver) is acceptable from a pharmacokinetic point of view, the applied strengths of the test product are considered bioequivalent with the corresponding strengths of the reference product.

Pharmacodynamics/Clinical efficacy/Clinical safety
No new studies on pharmacodynamics, clinical efficacy or clinical safety have been submitted. Since bioequivalence with the originator product has been demonstrated, additional data is not deemed necessary.

Risk Management Plan
The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Oxycodone/Naloxone Nordic Drugs.

Safety specification
The MAH has submitted the version 1.9 RMP dated 2024-02-12 and proposed the following summary safety concerns:

Summary of Safety Concerns	
Important identified risks	• Respiratory depression • Drug dependence and drug withdrawal syndrome • Overdose • Medication error • Constipation • Diarrhoea
Important potential risks	• Drug abuse, misuse and diversion • Hepatic disorders • Increased risk of withdrawal or overdose in patients with hepatic or renal failure
Missing information	• Use in paediatric patients <18 years • Use in pregnant and breastfeeding women • Off label use

Pharmacovigilance Plan

Routine pharmacovigilance is suggested and no additional pharmacovigilance activities are proposed by the applicant, which is endorsed.

Risk minimisation measures

Routine risk minimisation is suggested and no additional risk minimisation activities are proposed by the applicant, which is endorsed.

Summary of the RMP
The submitted Risk Management Plan, version 1.0 signed 2024-02-12 is considered acceptable.

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

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

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

V. USER CONSULTATION

A user consultation with target patient groups on the package information leaflet (PL) has been performed on the basis of a bridging report making reference to Oxycodone/Naloxone G.L. leaflet (DE/H/4650/001-005).

The bridging report submitted by the applicant has been found acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The quality of the generic product, Oxycodone/Naloxone Nordic Drugs, is found adequate. There are no objections to approval of Oxycodone/Naloxone Nordic Drugs, from a non-clinical and clinical point of view. Bioequivalence between the test and reference product has been adequately demonstrated. The product information is acceptable. The benefit/risk is considered positive, and the application is therefore recommended for approval.

List of recommendations not falling under Article 21a/22a/22 of Directive 2001/83/EC in case of a positive benefit risk assessment

N/A

List of conditions pursuant to Article 21a/22a or 22 of Directive 2001/83/EC

N/A

VII. APPROVAL

Oxycodone/Naloxone Nordic Drugs, 40 mg/20 mg, Prolonged-release tablet was approved in the national procedure on 2025-04-02.

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Public Assessment Report – Update

Procedure number*	Scope	Product Information affected (Yes/No)	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse

*Only procedure qualifier, chronological number and grouping qualifier (when applicable)

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