LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Public Assessment Report

Scientific discussion

Denephor
(oxycodone hydrochloride and naloxone hydrochloride dehydrate)

SE/H/1460/01-04/DC

This module reflects the scientific discussion for the approval of Denephor. The procedure was finalised on 2016-01-21. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

The application for Denephor, 5mg/2.5mg, 10mg/5mg, 20mg/10mg, 40mg/20mg, prolonged release tablet, is a generic application made according to Article 10(1) of Directive 2001/83/EC. The applicant, Acino AG applies through the Decentralised Procedure with Sweden acting as reference member state (RMS) and DE as concerned member state (CMS).

The reference medicinal product chosen for the purposes of establishing the expiry of the data protection period is Targin, 5 mg/2.5 mg; Targin, 10 mg/5 mg; Targin, 20 mg/10 mg; Targin, 40 mg/20 mg, prolonged release tablet, authorised in DE since 2006, with Mundipharma GmbH as marketing authorisation holder.

The reference product used in the bioequivalence study is Targinact 40mg/20mg, Targinact 20mg/10mg, Targinact 10mg/5mg and Targinact 5mg/2.5mg by tablet from UK with Napp Pharmaceuticals Limited as marketing authorisation holder.

For approved indications, see the Summary of Product Characteristics.

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

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

III.1 Discussion on the non-clinical aspects

Since this product has been shown to be essentially similar and refer to a product approved based on a full application with regard to preclinical data, no further such data have been submitted or are considered necessary.

IV. CLINICAL ASPECTS

IV.1 Pharmacokinetics

The applied products are prolonged release single unit formulations. The clinical development program was divided up in two packages, a lower dose package (oxycodone/naloxone 5mg/2.5mg and 10mg/5mg) and a higher dose package (oxycodone/naloxone 20mg/10mg and 40mg/20mg). The compositions are proportional for the upper strength pair 20mg/10mg and 40mg/20mg and for the lower strength pair 5mg/2.5mg and 10mg/5mg, respectively.

The applicant has performed 8 bioequivalence studies. One single dose study under fasting condition was performed for each strength. One single dose study under fed condition and one multiple dose study under fasting condition were performed for the highest strength in each strength pair (i.e. oxycodone/naloxone 40mg/20mg and 10mg/5mg). A single dose study has been performed for each strength and since the composition is proportional for each strength pair, a single dose study under fed condition and a multiple dose study under fasting condition on the highest strength in each strength pair are considered sufficient. Thus, the study packaged is considered sufficient. A summary of each bioequivalence study is given below.

Bioequivalence was established in all studies for oxycodone and naloxone-3-glucuronide. According to the SmPC of the originator Targiniq the oral bioavailability of naloxone is low (<3 %) and it is not possible to measure naloxone even when maximal dose is administrated. Thus, it seems difficult to establish bioequivalence based on naloxone and bioequivalence based on naloxone-3-glucuronide is found acceptable in all bioequivalence studies.

SINGLE DOSE CROSSOVER BIOEQUIVALENCE STUDY ON THE 40MG/20MG-STRENGTH UNDER FASTING CONDITION (STUDY C_21180_P1_03)

Bioequivalence was evaluated in one single-dose, two-way crossover study conducted in 36 healthy volunteers, comparing Oxycodone/Naloxone, 40mg/20mg, prolonged-release tablet with Targinact, 40mg/20mg, prolonged-release tablet under fasting conditions. The study was conducted at Algorithme Pharma Inc in Canada between 2013/02/24 and 2013/03/05. Blood samples were collected pre-dose and up to 36 hours post-dose. The study design is considered acceptable. Plasma concentrations of oxycodone and naloxone-3-glucuronide were determined with an LC/MS/MS method. For AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} the 90% confidence interval for the ratio of the test and reference products fell within the conventional acceptance range of 80.00-125.00% for both oxycodone and naloxone-3-glucuronide.

SINGLE DOSE CROSS-OVER BIOEQUIVALENCE STUDY ON THE 40MG/20MG STRENGTH UNDER FED CONDITIONS (C_21180_P1_04)

Bioequivalence was evaluated in one single-dose, two-way crossover study conducted in 40 healthy volunteers, comparing Oxycodon/Naloxon, 40mg/20mg, prolonged-release tablet with Targinact, 40mg/20mg, prolonged-release tablet under fed conditions. The study was conducted at Algorithme Pharma Inc in Canada between 30-Apr-2013 and 09-May-2013. Blood samples were collected pre-dose and up to 36 hours post-dose. The study design is considered acceptable. Plasma concentrations of oxycodone and naloxone-3-glucuronide were determined with an LC/MS/MS method. For AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} the 90% confidence interval for the ratio of the test and reference products fell within the conventional acceptance range of 80.00-125.00% for both oxycodone and naloxone-3-glucuronide.

MULTIPLE DOSE CROSS-OVER BIOEQUIVALENCE STYDY ON THE 40MG/20MG STRENGTH UNDER FASTING CONDITION (C_21180_P1_05)

Bioequivalence was evaluated in one multiple-dose, two-way crossover study conducted in 40 healthy volunteers, comparing Oxycodon/Naloxon, 40mg/20mg, prolonged-release tablet with Targinact, 40mg/20mg, prolonged-release tablet, under fasting conditions. The study was conducted at Algorithme Pharma Inc in Canada between 2013/10/04 and 2013/10/19. The first blood sample of each period was collected prior to the 1st naltrexone administration, within 5 minutes of the 3rd, 5th, 7th and 9th oxycodone /naloxone administration and up to 24 hours following the 9th oxycodone /naloxone administration. The study design is considered acceptable. Plasma concentrations of oxycodone and naloxone-3-glucuronide were determined with an LC/MS/MS method. For $AUC_{0-\tau}$, C_{max} and C_{τ} the 90% confidence interval for the ratio of the test and reference products fell within the conventional acceptance range of 80.00-125.00% for both oxycodone and naloxone-3-glucuronide.

SINGLE DOSE CROSSOVER BIOEQUIVALENCE STUDY ON THE 20MG/10MG STRENGTH UNDER FASTING CONDITION (C_21180_P1_06)

Bioequivalence was evaluated in one single-dose, two-way crossover study conducted in 36 healthy volunteers, comparing Oxycodon/Naloxon, 20mg/10mg, prolonged-release tablet with Targinact 20mg/10mg, prolonged-release tablet under fasting conditions. The study was conducted at Algorithme Pharma Inc in Canada between 2013/10/09 and 2013/10/18. Blood samples were collected pre-dose and up to 36 hours post-dose. The study design is considered acceptable. Plasma concentrations of oxycodone and naloxone-3-glucuronide were determined with an LC/MS/MS method. For $AUC_{0-t,}$ $AUC_{0-\infty}$ and C_{max} the 90% confidence interval for the ratio of the test and reference products fell within the conventional acceptance range of 80.00-125.00% for both oxycodone and naloxone-3-glucuronide.

SINGLE DOSE CROSSOVER BIOEQUIVALENCE STUDY ON THE 10MG/5MG STRENGTH UNDER FASTING CONDITION (C_21180_P1_07)

Bioequivalence was evaluated in one single-dose, two-way crossover study conducted in 36 healthy volunteers, comparing Oxycodon/Naloxon, 10mg/5mg, prolonged release tablet with Targinact, 10mg/5mg, prolonged-release tablet under fasting conditions. The study was conducted at Algorithme Pharma Inc in Canada between 2014/03/17 and 2014/03/26. Blood samples were collected pre-dose and up to 36 hours post-dose. The study design is considered acceptable. Plasma concentrations of oxycodone and naloxone-3-glucuronide were determined with an LC/MS/MS method. For $AUC_{0-t,}$ $AUC_{0-\infty}$ and C_{max} the 90% confidence interval for the ratio of the test and reference products fell within the conventional acceptance range of 80.00-125.00% for both oxycodone and naloxone-3-glucuronide.

SINGLE DOSE CROSSOVER BIOEQUIVAELNCE STUDY ON THE 10MG/5MG STRENGTH UNDER FED CONDITION (C_21180_P1_08)
Bioequivalence was evaluated in one single-dose, two-way crossover study conducted in 40 healthy volunteers, compairing Oxycodon/Naloxon, 10mg/5mg, prolonged-release tablet with Targinact, 10mg/5mg, prolonged-release tablet under fed conditions. The study was conducted at Algorithme Pharma Inc in Canada between 2014/01/05 and 2014/01/14. Blood samples were collected pre-dose and up to 36 hours post-dose. The study design is considered acceptable. Plasma concentrations of oxycodone and naloxone-3-glucuronide were determined with an LC/MS/MS method. For $AUC_{0-t,}$ $AUC_{0-\infty}$ and C_{max} the 90% confidence interval for the ratio of the test and reference products fell within the conventional acceptance range of 80.00-125.00% for both oxycodone and naloxone-3-glucuronide.

MULTIPLE DOSE CROSSOVER BIOEQUIVALENCE STUDY ON THE 10MG/5MG STRENGTH UNDER FASTING CONDITION (C_21180_P1_09)
Bioequivalence was evaluated in one multiple-dose, two-way crossover study conducted in 40 healthy volunteers, comparing Oxycodon/Naloxon, 10mg/5mg, prolonged release tablet with Targinact, 10mg/5mg, prolonged-release tablet under fasting conditions. The study was conducted at Algorithme Pharma Inc in Canada between 2014/03/19-2014/04/05. The first blood sample of each period was collected prior to the 1st naltrexone administration, while the others were collected within 5 minutes of the 3rd, 5th, 7th and 9th oxycodone/naloxone administration and up to 24 hours following the 9th oxycodone/naloxone administration. The study design is considered acceptable. Plasma concentrations of oxycodone and naloxone-3-glucuronide were determined with an LC/MS/MS method. For $AUC_{0-\tau}$, C_{max} and C_{τ} the 90% confidence interval for the ratio of the test and reference products fell within the conventional acceptance range of 80.00-125.00% for both oxycodone and naloxone-3-glucuronide.

SINGLE DOSE CROSSOVER BIOEQUIVALENCE STUDY ON THE 5MG/2.5MG STRENGTH UNDER FASTING CONDITION (C_21180_P1_10)
Bioequivalence was evaluated in one single-dose, two-way crossover study conducted in 36 healthy volunteers, comparing Oxycodon/Naloxon, 5mg/2.5mg, prolonged-release tablet with Targinact, 5mg/2.5mg, prolonged-release tablet under fasting conditions. The study was conducted at Algorithme Pharma Inc in Canada between 2014/01/19 and 2014/01/28. Blood samples were collected pre-dose and up to 36 hours post-dose. The study design is considered acceptable. Plasma concentrations of oxycodone and naloxone-3-glucuronide were determined with an LC/MS/MS method. For $AUC_{0-t,}$ $AUC_{0-\infty}$ and C_{max} the 90% confidence interval for the ratio of the test and reference products fell within the conventional acceptance range of 80.00-125.00% for both oxycodone and naloxone-3-glucuronide.

Bioequivalence between the test and reference products have been adequately demonstrated.

IV.2 Discussion on the clinical aspects

Since this product has been shown to be essentially similar and refer to a product approved based on a full application with regard to clinical efficacy/safety data, no further such data have been submitted or are considered necessary.

IV.3 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 Denephor.

Safety specification

Summary table of safety concerns as approved in RMP

Important identified risks	• Respiratory depression • Severe gastrointestinal disorders
Important potential risks	• Tolerance and dependence after long-term administration • Opioid withdrawal symptoms • CNS-depressant effect • Abuse/misuse/diversion • Interactions • Increased plasma levels in patients with hepatic/renal impairment • Long-term treatment of restless legs syndrome beyond 12 months • Safety and efficacy in pregnant and lactating women and newborn
Missing information	• NA

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 MAH has satisfactory responded to the questions raised and updated the RMP accordingly.

The RMP for the originator (Targiniq) has recently been updated. The MAHs have agreed to update their RMP accordingly once orginators RMP has been implemented.

The RMP is approved.

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

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

V. USER CONSULTATION

The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The language used for the purpose of user testing the PIL was English.
The results show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The quality of the generic product, Denephor, is found adequate. There are no objections to approval of Denephor, from a nonclinical and clinical point of view. Bioequivalence between the test and reference product has been adequately demonstrated. The product information is acceptable.

The application is therefore recommended for approval.

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

N/A

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

N/A

VII. APPROVAL

The Decentralised procedure for Denephor was positively finalised on 2016-01-21.

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Public Assessment Report – Update

Scope	Procedure number	Product Information affected	Date of start of the procedure	Date of end of procedure	Approval/ non approval	Assessment report attached
						Y/N (version)

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