CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

OxyNorm Instant 5 mg, 10 mg and 20 mg, orodispersible tablets Mundipharma Pharmaceuticals B.V., the Netherlands

oxycodone (as hydrochloride)

This assessment report is published by the MEB pursuant Article 21 (3) and (4) of Directive 2001/83/EC. The report comments on the registration dossier that was submitted to the MEB.
It reflects the scientific conclusion reached by the MEB at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation.
This report is intended for all those involved with the safe and proper use of the medicinal product, i.e. healthcare professionals, patients and their family and carers. Some knowledge of medicines and diseases is expected of the latter category as the language in this report may be difficult for laymen to understand.

This assessment report shall be updated by a following addendum whenever new information becomes available.

General information on the Public Assessment Reports can be found on the website of the MEB.

To the best of the MEB's knowledge, this report does not contain any information that should not have been made available to the public. The MAH has checked this report for the absence of any confidential information.

Registration number in the Netherlands: RVG 34775-34777

31 March 2011

Pharmacotherapeutic group:	natural opium alkaloids
ATC code:	N02AA05
Route of administration:	oral
Therapeutic indication:	management of severe pain requiring treatment with a strong opioid
Prescription status:	prescription only
Date of authorisation in NL:	10 June 2010
Application type/legal basis:	Directive 2001/83/EC, Article 8(3)

For product information for healthcare professionals and users, including information on pack sizes and presentations, see Summary of Product Characteristics (SPC), package leaflet and labelling.

I INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Medicines Evaluation Board of the Netherlands (MEB) has granted a marketing authorisation for OxyNorm Instant 5 mg, 10 mg and 20 mg, orodispersible tablets from Mundipharma Pharmaceuticals B.V. The date of authorisation was on 10 June 2010 in the Netherlands.

The product is indicated for management of severe pain requiring treatment with a strong opioid.

A comprehensive description of the indications and posology is given in the SPC.

Oxycodone is a full opioid agonist with no antagonist properties. It has an affinity for kappa, mu and delta opiate receptors in the brain, spinal cord and peripheral organs (e.g. intestine). Oxycodone acts as opioid-receptor agonist at these receptors and affects pain relief by binding to the endogenous opioid receptors in the CNS. The therapeutic effect is mainly analgesic, anxiolytic and sedative.

This national procedure concerns a line extension to oxycodone immediate-release capsules 5,10, 20 mg, Oxynorm® (NL License RVG 27509-27511) by Mundipharma, which have been registered in the Netherlands since 9 December 2002. Furthermore, reference is made to the original dossier of OxyContin prolonged-release tablets, which were first registered in the Netherlands in 1997. With this application an additional immediate-release pharmaceutical form is introduced: an orodispersible tablet in addition to the previously authorised capsules.

This national procedure concerns a so-called full dossier application according to Article 8(3) of Directive 2001/83/EC, a dossier with administrative, chemical-pharmaceutical, pre-clinial and clinical data.
The active component of OxyNorm Instant 5 mg, 10 mg and 20 mg, orodispersible tablets is considered to be well-known and the clinical pharmacology of oxycodone has been extensively studied. Parts of the data in the dossier of Oxynorm Instant orodispersible tablets were already submitted in the dossiers of oxycodone immediate-release capsules 5,10, 20 mg, Oxynorm® (NL License RVG 27509-27511).
The MAH submitted a bioequivalence study in which the pharmacokinetic profile of the proposed 20 mg product is compared with the pharmacokinetic profile of the original product Oxynorm 20 mg capsules, obtained from the UK. A bioequivalence study is the widely accepted means of demonstrating that difference of the formulation and different methods of manufacture have no influence on efficacy and safety. The orodispersible tablet can be used instead of the capsule.

No scientific advice has been given to the MAH with respect to these products and no paediatric development programme has been submitted, as this is not required for a line extension.

II SCIENTIFIC OVERVIEW AND DISCUSSION

II.1 Quality aspects

Compliance with Good Manufacturing Practice
The MEB has been assured that acceptable standards of GMP (see Directive 2003/94/EC) are in place for these product types at all sites responsible for the manufacturing of the active substance as well as for the manufacturing and assembly of this product prior to granting its national authorisation.

Active substance
The active substance is oxycodone, an established active substance described in the European Pharmacopoeia (Ph.Eur.*). The substance is a white to off-white, hygroscopic powder, which is soluble in water and slightly soluble in alcohol.

The CEP procedure is used for the active substance. Under the official Certification Procedures of the EDQM of the Council of Europe, manufacturers or suppliers of substances for pharmaceutical use can apply for a certificate of suitability concerning the control of the chemical purity and microbiological quality of their substance according to the corresponding specific monograph, or the evaluation of reduction of Transmissible Spongiform Encephalopathy (TSE) risk, according to the new general monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the European Pharmacopoeia.

Manufacturing process
A CEP has been submitted; therefore no details on the manufacturing process have been included.

Quality control of drug substance
The active substance specification is considered adequate to control the quality and meets the requirements of the monograph in the Ph.Eur. and the CEP, with additional requirements for a limit for unknown individual impurities and a limit for particle size distribution.
Batch analytical data demonstrating compliance with this specification have been provided for 5 batches.

Stability of drug substance
The active substance is stable for 5 years when stored under the stated conditions. Assessment thereof was part of granting the CEP and has been granted by the EDQM.

** Ph.Eur. is an official handbook (pharmacopoeia) in which methods of analysis with specifications for substances are laid down by the authorities of the EU.*

Medicinal Product

Composition
OxyNorm Instant 5 mg, 10 mg and 20 mg are white to off-white round, flat, bevelled edge orodispersable tablets marked with ‘O’ on one side and ‘5’, ‘10’ and ‘20’ respectively, on the other.
The products contain 5, 10 or 20 mg oxycodone hydrochloride corresponding to 4.5 mg, 9 mg and 18 mg oxycodone, respectively.

The orodispersible tablets are packed in aluminium/aluminium blisters.

The excipients are: sugar spheres, polyacrylate dispersion 30%, hypromellose, mannitol (E421), silicon dioxide, microcrystalline cellulose, crospovidone, aspartame (E951), spearmint flavour, magnesium stearate.
The composition of the different strengths is dose proportional.

Pharmaceutical development

Pharmaceutical development is in general satisfactorily described, e.g. the purposes of the several excipients and the purpose and development of the dosage form of the formulation are sufficiently described. The orodispersable tablets are introduced to facilitate administration: after rapid dispersion in the mouth, they are to be swallowed, without the use of water. This is seen as a useful addition to the registered immediate-release capsules, which are available in the same strengths.
A bioequivalence study has been submitted between the 20 mg tablet strength of the proposed product and the 20 mg strength of the authorised immediate-release capsules, obtained from the UK. The formulation of these UK Oxynorm capsules is identical to the innovator product registered in the Netherlands.
From a chemical-pharmaceutical point of view the proposed product can be regarded as essentially similar to the registered capsules in the Netherlands.

Manufacturing process
The manufacturing process has been adequately described in the dossier and comprises preparation of the coated oxycodone hydrochloride granules and preparation of the tableting mixture, tableting and packaging. The manufacturing process comprises a standard process. Appropriate data have been provided to validate the process for the finished product.

Control of excipients
Except for silicon dioxide and spearmint flavour all excipients comply with Ph.Eur. requirements. These specifications are acceptable.

Quality control of drug product
Control of the drug product is satisfactory documented. The specification includes tests for description, average mass, uniformity of dosage units, identification and content of oxycodone hydrochloride, disintegration time, dissolution test, impurities content, microbiological quality and total viable aerobic count. The limits have been sufficiently qualified. The analytical methods have been adequately described and validated.
Batch analysis data on three production-scale batches of each tablet strength manufactured at the proposed production site have been provided, demonstrating compliance with the release specification.

Stability of drug product
Stability data on the product have been provided for three batches of 5 mg and 20 mg product stored at 25°C/60%RH (36 months) and 40°C/75% RH (6 months). The product was packed in the proposed blister pack. No significant trends or changes were observed. All results remained within the shelf-life limits.
For the 10 mg tablet a sufficiently justified bracketing design is used. The results of the stability studies are extrapolated to this strength.
Photostability testing was conducted in accordance with the applicable Note for Guidance. The results demonstrate that there was no significant degradation after light exposure. Besides, the aluminium blister prevents influence of light.
Based on the results provided, a shelf life of 3 years without specific storage condition was granted.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
There are no substances of ruminant animal origin present in the product nor have any been used in the manufacturing of this product, so a theoretical risk of transmitting TSE can be excluded.

II.2 Non-clinical aspects

This product is a line extension to Oxynorm capsules, which is available on the European market. No new preclinical data have been submitted. The MAH referred to the preclinical documentation included in the application for the immediate-release capsules, as well as the OxyContin prolonged-release tablets. Therefore the application has not undergone additional preclinical assessment. This is acceptable for this type of application.

Environmental risk assessment

A justification for the absence of an Environmental risk assessment (ERA) was required and presented by the MAH. The potential risks of the expected use of oxycodone hydrochloride orodispersible tablets to the environment following marketing approval in the European Union have been assessed in a step-wise procedure. It was determined that the assessment should be based on the active ingredient, oxycodone HCl, and its expected presence in the aquatic compartment of the environment. The predicted environmental concentrations in the aquatic compartment were calculated as recommended in the "Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use" (EMEA/CHMP/SWP/4447/00). The 'worst-case' calculated, predicted environmental concentrations (surface water) for oxycodone HCl exceeded the Phase II trigger value. However, the maximum dose prescribed for this oxycodone product is similar to the other oxycodone products. It is therefore expected that the use of the orodispersible tablet will replace other available oxycodone products, and thus the amount of active substance emitted to the environment is not expected to increase.

II.3 Clinical aspects

Oxycodone is a well-known active substance with established efficacy and tolerability.

No new clinical data have been submitted. The MAH referred to the clinical documentation included in the dossier of the immediate-release capsules and prolonged-release tablets. But for this line extension, the MAH submitted a bioequivalence study in which the pharmacokinetic profile of the test product OxyNorm Instant 20 mg orodispersible tablets (Mundipharma Pharmaceuticals B.V., NL) is compared with the pharmacokinetic profile of the reference product Oxynorm 20 mg capsules (Napp Pharmaceuticals Ltd, UK).

The choice of the reference product
The choice of the reference product in the bioequivalence study has been justified by comparison of dissolution results and compositions of Oxynorm capsules.
The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Design
A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 28 healthy subjects (13 females/15 males), aged 22-54 years. Each subject received a single dose (20 mg) of one of the 2 oxycodone formulations. After a supervised overnight fast, an oral dose of naltrexone (1 x 50 mg tablet) was administered with 240 ml of water approximately 2 hours before oxycodone administration. For the test product, subjects had to let the tablet completely disperse in the mouth (for about 2 minutes) before swallowing the saliva; no water was provided. For the reference formulation, subjects had to swallow the tablet with 240 ml of water. There were 2 dosing periods, separated by a washout period of 7 days.

Blood samples were collected pre-dose and at 0.25, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.5, 3, 4, 6, 8, 10, 12, 16 and 24 hours after administration of the products.

Analytical/statistical methods
The analytical method has been adequately validated and is considered acceptable for analysis of the plasma samples. The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

Results
Four subjects withdrew their consent for personal reasons. One subject was withdrawn for pharmacokinetic reasons (not eating lunch). The 23 remaining subjects completed the study and were eligible for pharmacokinetic analysis.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean, t_{max} (median, range)) of oxycodone under fasted conditions.

Treatment N=23	AUC_{0-t} ng.h/ml	$AUC_{0-\infty}$ ng.h/ml	C_{max} ng/ml	t_{max} h	$t_{1/2}$ h
Test	232.9	237.5	49.9	1.25 (0.75-4.00)	4.00
Reference	226.2	230.0	49.3	1.00 (0.5-2.50)	4.01
***Ratio (90% CI)**	1.03 (0.98-1.08)	1.03 (0.98-1.09)	1.01 (0.93-1.11)	--	--
CV (%)	10.0	9.8	17.4	--	--

$AUC_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity
AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours
C_{max} maximum plasma concentration
t_{max} time for maximum concentration
$t_{1/2}$ half-life

**ln-transformed values*

The 90% confidence intervals calculated for AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} are in agreement with those calculated by the MAH and are within the bioequivalence acceptance range of 0.80-1.25. Based on the pharmacokinetic parameters of oxycodone under fasted conditions, it can be concluded that OxyNorm Instant 20 mg orodispersible tablets and Oxynorm 20 mg capsules are bioequivalent with respect to rate and extent of absorption, and fulfil the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

Oxycodone may be taken without reference to food intake. From the literature it is known that food does not interact with the absorption of oxycodone. Therefore, a food interaction study is not deemed necessary. The bioequivalence study under fasting conditions is in accordance with CPMP/EWP/QWP/1401/98 Note for Guidance on the investigation of bioavailability and bioequivalence.

Extrapolation to other strengths
The dissolution profile shows that the test product is highly soluble (>96% is dissolved within 15 min). Oxycodone displays linear kinetics. The different tablets have a dose-proportional composition. Therefore, the results of the bioequivalence study with the 20 mg strength can be extrapolated to the 5 mg and 10 mg orodispersible tablets.

The MEB has been assured that the bioequivalence study has been conducted in accordance with acceptable standards of Good Clinical Practice (GCP, see Directive 2005/28/EC) and Good Laboratory Practice (GLP, see Directives 2004/9/EC and 2004/10/EC).

Safety conclusion
No new safety concerns has been raised since the the registration of the tablets.

Risk management plan
Oxycodone was first approved in 1995, and there is now more than 10 years post-authorisation experience with the active substance. The MAH has a pharmacovigilance system at their disposal, which is based on the current European legislation. Besides routine pharmacovigilance activities, the Risk management plan comprises the following:

Prolongation of QTc	No evidence for association. Continue routine pharmacovigilance activities.	No risk minimisation activities required.
Interaction with Gabapentin/Pregabalin	No evidence for association. Continue routine pharmacovigilance activities.	Update to CCDS/SPC if evidence for interaction identified.
Oxycodone hydrochloride overdose	Routine pharmacovigilance activities to monitor for changes in frequency or identify at risk groups	Ongoing risk minimisation activities; - Proper patient selection - Communication of product safety -Child safety - Special warnings and precautions for use - Restricting marketing authorisation conditions - Restricting prescribers - Controlled drug status - Ampoule ring design
Oxycodone hydrochloride abuse, misuse, diversion, drug assisted crime	Routine pharmacovigilance activities to monitor for changes in frequency, monitor for drug-assisted crime or identify at risk groups.	Ongoing risk minimisation activities; - Proper patient selection - Communication of product safety - Child safety - Special warnings and precautions for use - Restricting marketing authorisation conditions - Restricting prescribers - Controlled drug status

		- Restricting prescribers
Oxycodone hydrochloride off-label use	Routine pharmacovigilance activities to monitor for changes in frequency or identify at risk groups	Ongoing risk minimisation activities; - Proper patient selection - Communication of product safety - Child safety - Contraindications and special warnings and precautions for use - Restricting marketing authorisation conditions - Restricting prescribers -- Controlled drug status

Oxycodone hydrochloride dependence and withdrawal	Routine pharmacovigilance activities to monitor for changes in frequency or identify at risk groups	Ongoing risk minimisation activities; - Proper patient selection - Communication of product safety - Special warnings and precautions for use - Restricting marketing authorisation conditions - Restricting prescribers - Controlled drug status
Oxycodone hydrochloride medication errors	Routine pharmacovigilance activities to monitor for changes in frequency or identify at risk	Ongoing risk minimisation activities; - Proper patient selection

	groups	- Communication of product safety - Contraindications and special warnings and precautions for use - Restricting marketing authorisation conditions -- Restricting prescribers - Ampoule ring design
Oxycodone hydrochloride use in children and adolescents	Routine and focused pharmacovigilance activities.	Ongoing risk minimisation activities; - Proper patient selection - Communication of product safety - Restricting marketing authorisation conditions - Restricting prescribers
Oxycodone hydrochloride use during pregnancy or lactation	Routine and focused pharmacovigilance activities.	Ongoing risk minimisation activities; - Proper patient selection - Communication of product safety - Restricting marketing authorisation conditions - Restricting prescribers -Focused follow-up requests of pregnancy cases.

Product information

SPC, PIL and labelling

The content of the SPC approved during the national procedure is in accordance with those accepted for other oxycodone products. A warning with regard to concomitant alcohol use has been included in the PIL and labelling in accordance with the CMD(h) recommendation.

Readability test

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 test consisted of a pilot test with 4 participants, followed by two rounds with 10 participants each. Fifteen questions were asked. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability.

The results of two rounds of testing show that almost 100% of the participants could find the required information and was able to answer correctly. The PIL was amended after the pilot test, in between test rounds and after the second round. These modifications were mainly based on recommendations from the participants. The readability test has been sufficiently performed.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

OxyNorm Instant 5 mg, 10 mg and 20 mg, orodispersible tablets have a proven chemical-pharmaceutical quality and are approvable line extensions to Oxynorm capsules. Oxynorm capsules is a well-known medicinal product with an established favourable efficacy and safety profile.

For this application the MAH refers to the registration file of Oxynorm® (NL License RVG 27509-27511). Additionally bioequivalence has been demonstrated between the orodispersible tablets and immediate-release capsules. The bioequivalence study showed to be in compliance with the requirements of European guidance documents. The MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

The SPC, package leaflet and labelling are in the agreed templates and are in agreement with other oxycodone containing products.

The Board followed the advice of the assessors. The MEB, on the basis of the data submitted, considered that efficacy and safety has been shown and that essential similarity has been demonstrated with the oxycodone immediate-release capsules 5,10, 20 mg, Oxynorm® (NL License RVG 27509-27511) from Mundipharma Pharmaceuticals B.V. Therefore, the Board granted a marketing authorisation. OxyNorm Instant 5 mg, 10 mg and 20 mg, orodispersible tablets was authorised in the Netherlands on 10 June 2010.

There were no post-approval commitments made during the procedure.

List of abbreviations

ASMF	Active Substance Master File
ATC	Anatomical Therapeutic Chemical classification
AUC	Area Under the Curve
BP	British Pharmacopoeia
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
C_{max}	Maximum plasma concentration
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CV	Coefficient of Variation
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
ERA	Environmental Risk Assessment
EU	European Union
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
MEB	Medicines Evaluation Board in the Netherlands
OTC	Over The Counter (to be supplied without prescription)
PAR	Public Assessment Report
Ph.Eur.	European Pharmacopoeia
PIL	Package Leaflet
PSUR	Periodic Safety Update Report
SD	Standard Deviation
SPC	Summary of Product Characteristics
$t_{½}$	Half-life
t_{max}	Time for maximum concentration
TSE	Transmissible Spongiform Encephalopathy
USP	Pharmacopoeia in the United States

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Scope	Procedure number	Type of modification	Date of start of the procedure	Date of end of the procedure	Approval/ non approval	Assessment report attached