CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

OxyContin 15 mg, 30 mg, 60 mg, 120 mg and 160 mg, prolonged-release tablets Mundipharma Pharmaceuticals B.V., the Netherlands

oxycodone

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 100819-100821, 100824-100825

4 September 2013

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:	4 May 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 OxyContin 15 mg, 30 mg, 60 mg, 120 mg and 160 mg, prolonged-release tablets from Mundipharma Pharmaceuticals B.V. The date of authorisation was on 4 May 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.
A comprehensive description of the indications and posology is given in the SPC.

This national procedure concerns a line extension to OxyContin prolonged-release tablets 5, 10, 20, 40 and 80 mg, (NL License RVG 27536, 22107-22110) by Mundipharma, which have been registered in the Netherlands since 10 April 2000 (10/20/40/80 mg) and 15 July 2002 (5 mg). With this application 5 additional strengths are introduced.

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 OxyContin 15 mg, 30 mg, 60 mg, 120 mg and 160 mg prolonged-release tablets is considered to be well-known and the clinical pharmacology of oxycodone has been extensively studied. Parts of the data in the dossier were already submitted in the dossiers of OxyContin 5, 10, 20, 40 and 80 mg.
The MAH submitted two pharmacokinetic studies to support the line extension. These were conducted in healthy volunteers in order to compare bioequivalence between new formulations and strengths to the standard formulation of 40 and 80 mg. In addition, the MAH referred to several other PK and clinical studies that have been reviewed by the MEB in previous dossiers.

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
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
OxyContin 15 mg are round, biconvex, grey film-coated tablets with OC on one side and 15 on the other side.
OxyContin 30 mg are round, biconvex, brown film-coated tablets with OC on one side and 30 on the other side.
OxyContin 60 mg are round, biconvex, red film-coated tablets with OC on one side and 60 on the other side.
OxyContin 120 mg are round, biconvex, purple film-coated tablets with OC on one side and 120 on the other side.
OxyContin 160 mg are capsule-shaped, biconvex, blue film-coated tablets with OC on one side and 160 on the other side.

The prolonged-release tablets are packed in PVC blister packs with aluminium backing foil.

The excipients are:
Tablet core – lactose monohydrate, povidone, ammonio methacrylate copolymer dispersion, triacetin, stearyl alcohol, talc, magnesium stearate
Coating - hypromellose (E464), titanium dioxide (E171), macrogol, iron oxide (except 160 mg), polysorbate 80 (except 15 mg), indigo carmine lake (only 160 mg).

Pharmaceutical development
The development of the product has been described, the choice of excipients is justified and their functions explained. The proposed 15 mg, 30 mg, 60 mg, 120 mg and 160 mg strengths have the same qualitative formulation as that for the currently marketed strengths and are produced using the same method of manufacture. Therefore only limited formulation development was necessary, as for each strength the lubricated granules used were the same as for one of the marketed strengths of oxycodone hydrochloride prolonged-release tablets. Furthermore, the formulations of the 15 mg, 30 mg and 60 mg granules are identical to the corresponding granules for respectively the 10 mg, 20 mg and 40 mg registered product strengths. The 60, 80 and 120 mg formulations are dose proportional. The development of the 160 mg tablet has also been adequately described.
Comparative dissolution data is provided for different batches of all strengths. Reference is also made to a previously assessed IVIV-c (in-vitro-in-vivo correlation) report, which has confirmed a correlation between the *in vitro* dissolution data and the *in vivo* plasma concentration data for the 5 mg, 10 mg, 20 mg, 40 mg, 80 mg and 160 mg OxyContin tablet strengths.

Manufacturing process
The tablets are manufactured by wet granulation and subsequently coated. One production location is used. The tablet compression, coating steps and processes for the production of these are based on those applied to the manufacture of the currently marketed strengths.
The manufacturing process has been adequately validated according to relevant European guidelines. Sufficient validation data has been submitted in view of the already approved tablet strengths.

Control of excipients
The excipients comply with the Ph. Eur. or in-house specifications (Opadry coating). These specifications are acceptable.

Quality control of drug product
The product specification includes tests for description, hardness, identification, assay, uniformity of content, related substances, identification for dyes, dissolution and microbiological quality. The release and shelf life specifications are similar. The proposed specifications are acceptable.
The analytical methods have been adequately described and validated. Batch analytical data from the proposed production site has been provided on three full-scale batches of each strength, demonstrating compliance with the release specification.

Stability of drug product
Stability data on the product has been provided for three full-scale batches per strength stored at 25ºC/60%RH, 30ºC/65%RH and 40ºC/75%RH. The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in PVC blister packs with aluminium backing foil, assembled into cardboard cartons. Sufficient stability data is submitted to support the proposed shelf life of 3 years and storage condition ‘store below 25ºC’.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
The milk used to manufacture the lactose monohydrate, is sourced from healthy animals under the same conditions as milk collected for human consumption. All other excipients, including the components of the film coat, are not of animal origin.

II.2 Non-clinical aspects

This product is a line extension to OxyContin 5, 10, 20, 40 and 80 mg, prolonged-release tablets which are available on the European market. No new preclinical data have been submitted. The MAH referred to the preclinical documentation included in the immediate 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" (EMA/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 other oxycodone products. It is therefore expected that the use of additional strengths of the prolonged-release tablets 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.

The MAH performed two studies to support the line extension: one study where linearity of the new 15/30/60/120 mg tablet was compared to the standard 40 mg tablet in healthy volunteers, and one study to test whether the new 160 mg tablet was bioequivalent to two standard 80 mg tablets or four standard 40 mg tablets.

The choice of the reference product
The choice of the reference product in the bioequivalence studies has been justified. The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Bioequivalence study I - 15/30/60/120 mg vs. 40 mg tablet
Design
A single-dose, randomised, five-period, five-treatment, crossover bioequivalence study was carried out under fasted conditions in 29 healthy male subjects. Each subject received a single dose of one of the oxycodone formulations according to the following scheme:
A. 1 x Oxycodone HCl PR tablet 15 mg in a fasted state
B. 1 x Oxycodone HCl PR tablet 30 mg in a fasted state
C. 1 x Oxycodone HCl PR tablet 60 mg in a fasted state
D. 1 x Oxycodone HCl PR tablet 120 mg in a fasted state
E. Reference: 1 x Oxycodone HCl PR tablet 40 mg in a fasted state

There were 5 dosing periods, separated by a washout period of 7 days. Blood samples were collected pre-dose and at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 10, 12, 16, 24, 36, 48, and 72 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
Three subjects out of the planned 30 discontinued the study due to 3 separate reasons: adverse events (n=1, fracture right thumb) subject's choice (n=1) and administrative reasons (n=1). Twenty-seven

subjects were eligible for pharmacokinetic analysis. The results are presented in the tables and figure below.

Oxycodone results

Table 9. OIS1001 Summary Statistics for Oxycodone AUCt, AUCINF and Cmax, by Treatment

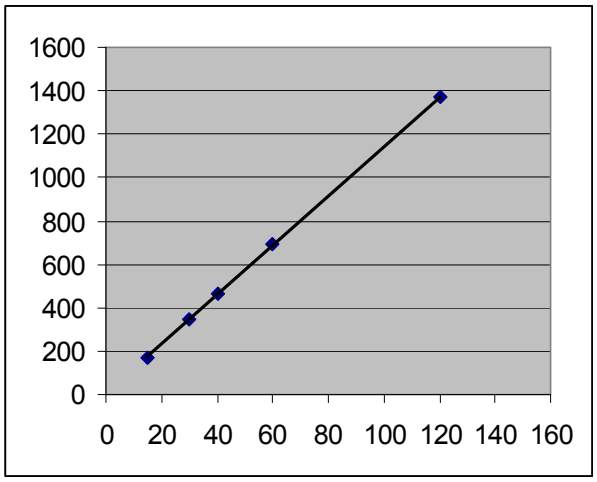
Cross-reference Table 14.4.2

		Study Treatment: Tablet Strength				
PK Metrics	Statistics	15 mg	30 mg	40 mg	60 mg	120 mg
AUCt (ng.h/mL)	n	29	27	28	28	26
	Geometric Mean	172.3	350.1	461.7	693.6	1369.8
	Geometric SE	1.04	1.04	1.04	1.04	1.04
	Exponentiated LS Mean	171.1	352.6	460.4	689.6	1381.9
AUCINF (ng.h/mL)	n	28	27	28	27	26
	Geometric Mean	175.1	352.7	465.0	701.3	1376.0
	Geometric SE	1.04	1.04	1.04	1.04	1.04
	Exponentiated LS Mean	173.2	355.2	463.6	696.0	1388.0
Cmax (ng/mL)	n	29	27	28	28	26
	Geometric Mean	15.03	29.58	36.95	59.78	106.65
	Geometric SE	1.030	1.033	1.032	1.032	1.038
	Exponentiated LS Mean	14.98	29.65	37.02	59.63	107.63

Cross-Reference: Appendix 16.10.2
21MAY2007:10:00 R:\MRD\Data Management & Statistics\SAS\OIS1001\Statistik\TLF\PKPD.txt

		Oxycodone		Noroxycodone		Oxymorphone		Noroxymorphone	
Parameter (Unit)	Tablet Strength vs. 40 mg	Test/ Reference (%)	90% Confidence Interval	Test/ Reference (%)	90% Confidence Interval	Test/ Reference (%)	90% Confidence Interval	Test/ Reference (%)	90% Confidence Interval
AUCt (ng.h/mL)	15 mg	99.1	[95.4, 102.9]	98.0	[95.1, 100.9]	49.6	[41.9, 58.7]	147.4	[139.9, 155.3]
	30 mg	102.1	[98.3, 106.2]	101.6	[98.6, 104.7]	87.3	[73.7, 103.4]	111.5	[105.7, 117.6]
	60 mg	99.9	[96.1, 103.8]	104.1	[101.0, 107.2]	113.1	[95.7, 133.8]	92.4	[87.6, 97.4]
	120 mg	100.1	[96.2, 104.0]	105.4	[102.2, 108.6]	135.1	[113.9, 160.2]	82.7	[78.4, 87.3]
AUCINF (ng.h/mL)	15 mg	99.6	[95.9, 103.5]	99.1	[96.2, 102.0]			152.6	[144.2, 161.4]
	30 mg	102.2	[98.3, 106.2]	102.7	[99.7, 105.9]	94.2	[77.9, 114.0]	112.7	[107.0, 118.8]
	60 mg	100.1	[96.3, 104.0]	103.8	[100.8, 106.9]	87.5	[73.4, 104.3]	91.2	[86.6, 96.0]
	120 mg	99.8	[96.0, 103.7]	104.5	[101.4, 107.7]	102.7	[89.7, 117.6]	79.6	[75.5, 83.9]
Cmax (ng/mL)	15 mg	107.9	[102.5, 113.6]	103.0	[98.9, 107.3]	108.3	[100.3, 117.0]	209.3	[193.2, 226.7]
	30 mg	106.8	[101.3, 112.5]	106.1	[101.8, 110.6]	107.4	[99.4, 115.9]	125.3	[115.5, 135.9]
	60 mg	107.4	[102.0, 113.1]	105.3	[101.1, 109.8]	108.0	[100.1, 116.5]	80.9	[74.6, 87.7]
	120 mg	96.9	[91.9, 102.2]	100.4	[96.3, 104.7]	102.0	[94.4, 110.2]	57.5	[53.0, 62.5]

AUC_{0-t} (geometric mean) Oxycodone versus dose



The 90% confidence intervals calculated for AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} of oxycodone are within the bioequivalence acceptance range of 0.80-1.25 for all strengths. Pharmacokinetics of oxycodone is dose linear between 15-120 mg. The mean half-life values and median t_{max} values for oxycodone were very similar for each of the treatments.

Differences were observed in BE of the metabolites. The major metabolite of oxycodone (noroxycodone) is less than 1/100 the potency of the parent compound. Another metabolite, oxymorphone, is pharmacologically active but produced in very small concentrations. The observed differences are therefore not considered relevant.

Based on the pharmacokinetic parameters of oxycodone under fasted conditions, it can be concluded that OxyContin 15 mg, 30 mg, 60 mg and 120 mg prolonged-release tablets are bioequivalent to the established Oxycontin® formulation of 40 mg with respect to rate and extent of absorption and that PK is dose-linear in this dose range. This study fulfils the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

Safety
The overall incidence of AEs was similar across all oxycodone tablet strengths (from 15 to 120 mg). There was no apparent relationship between the incidence of AEs and oxycodone dose. The most commonly occurring AEs were headache, nausea and abdominal pain. These types of AE are typically associated with strong opioid administration to opioid-naïve subjects.
One SAE (fractured thumb) occurred during the study. A subject suffered a fracture to his right thumb on Day 28 of the study, 6 days after receiving 15 mg oxycodone tablet in Study Period 4. This SAE was considered unrelated to the administration of study drug.
One subject had a clinically significant ECG finding (QTc interval prolongation) at the end of study. This had resolved 4 days later at follow-up. There were no clinically important changes in mean laboratory values or vital signs between baseline and end of study.

<u>Bioequivalence study II - 160 mg vs. 40 mg and 80 mg tablet</u>
Design
The pharmacokinetics of one 160 mg tablet, two 80 mg tablets and four 40 mg tablets of OxyContin were compared in a single-dose, randomised, crossover study. A total of 25 healthy male volunteers received each of the three treatments as a single dose after an overnight fast. In view of the high doses involved, the volunteers were also administered naltrexone HCl.

TABLE 2.0A
Study OC97-0301
Summary of Pharmacokinetic Parameters for Single Doses of One OxyContin® 160 mg Tablet, Two OxyContin® 80 mg Tablets, and Four OxyContin® 40 mg Tablets.

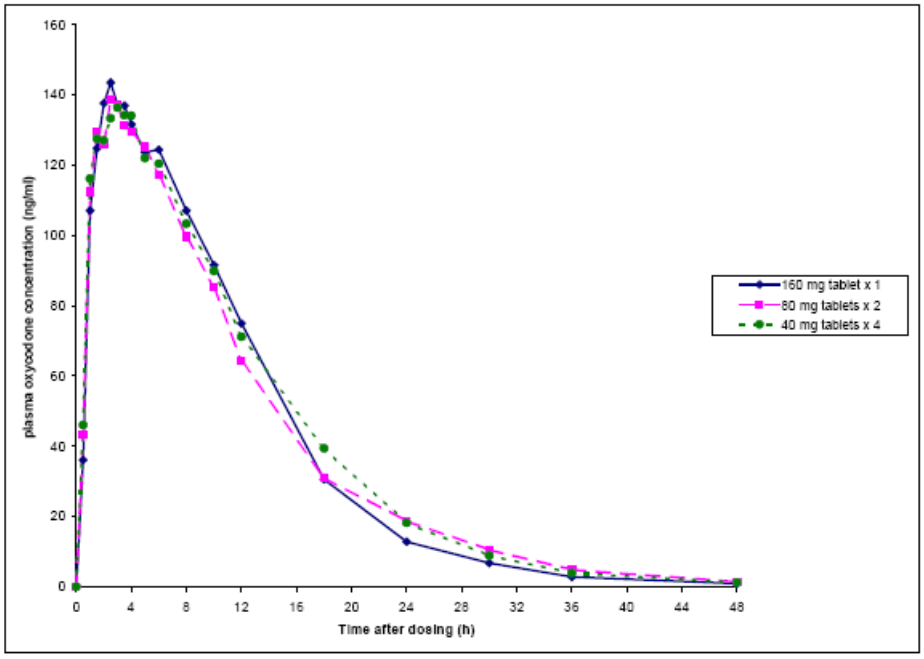
Parameter	OxyC 160 mg	OxyC 2×80 mg	OxyC 160 mg/2×80 mg[a] (%)	90% CI[a] Lower	90% CI[a] Upper
$AUC_{0\text{-last}}$ (ng•hr/mL)[b]	1757.16	1768.27	99.47	95.47	103.64
$AUC_{0\text{-}\infty}$ (ng•hr/mL)[b]	1764.10	1778.49	99.29	95.29	103.46
C_{max} (ng/mL) [b]	151.14	148.19	101.87	96.84	107.16
T_{max} (hr)[c]	2.54	2.78	91.37	71.66	113.89
$T_{½}$ abs (hr)[c]	1.38	1.27	108.25	88.04	127.73
$T_{½}$ elim (hr)[c]	5.15	5.45	94.49	86.34	102.73
W_{50} (hr)[c]	10.45	9.24	113.11	106.26	119.95

	OxyC 160 mg	OxyC 4×40 mg	OxyC 160 mg/4×40 mg[a] (%)	90% CI[a] Lower	90% CI[a] Upper
$AUC_{0\text{-last}}$ (ng•hr/mL)[b]	1757.16	1824.33	96.78	92.89	100.84
$AUC_{0\text{-}\infty}$ (ng•hr/mL)[b]	1764.10	1832.66	96.72	92.83	100.78
C_{max} (ng/mL) [b]	151.14	146.06	103.88	98.75	109.28
T_{max} (hr)[c]	2.54	2.56	99.22	76.88	122.18
$T_{½}$ abs (hr)[c]	1.38	1.28	107.18	87.44	126.86
$T_{½}$ elim (hr)[c]	5.15	5.70	90.34	82.60	98.29
W_{50} (hr)[c]	10.45	10.90	95.83	90.20	101.82

	OxyC 2×80 mg	OxyC 4×40 mg	OxyC 2×80 mg/4×40 mg[a] (%)	90% CI[a] Lower	90% CI[a] Upper
$AUC_{0\text{-last}}$ (ng•hr/mL)[b]	1768.27	1824.33	97.30	93.39	101.37
$AUC_{0\text{-}\infty}$ (ng•hr/mL)[b]	1778.49	1832.66	97.41	93.49	101.50
C_{max} (ng/mL) [b]	148.19	146.06	101.97	96.93	107.27
T_{max} (hr) [c]	2.78	2.56	108.59	84.63	129.92
$T_{½}$ abs (hr) [c]	1.27	1.28	99.01	79.60	119.02
$T_{½}$ elim (hr) [c]	5.45	5.70	95.61	87.84	103.52
W_{50} (hr)[c]	9.24	10.90	84.72	79.08	90.70

(Cross-Reference: Tables 14.4.2 to 14.4.9, and Appendix 16.2.5.2)
[a]Ratio and 90% confidence intervals are based on least square means.
Ratio (%) =Test mean / Reference mean x 100%.
[b]Geometric mean
[c]Arithmetic mean
N=25

Figure 2.5.3.2 Mean plasma oxycodone concentration over time (OC97-0301)



The 90% confidence intervals calculated for AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} of oxycodone are within the bioequivalence acceptance range of 0.80-1.25, indicating a comparable extent and rate of absorption. Pharmacokinetics of oxycodone is dose linear between 15-120 mg. The mean half-life values and median t_{max} values for oxycodone were very similar for each of the treatments.

The extent (AUC) and rate (C_{max}) of absorption indicate that all three dosage forms are bioequivalent. The t_{max} was slightly longer for the two 80 mg tablets (2.8 h) than for the 160 mg tablet (2.5 h) and four 40 mg tablets (2.6 h), and the t½ abs slightly longer for the 160 mg tablet (1.4 h) than for the two reference treatments (both 1.3 h). These differences were not considered to be of any clinical significance. The results from the study demonstrate that one 160 mg tablet is bioequivalent to two 80 mg and to four 40 mg strength tablets.

The MEB has been assured that the bioequivalence studies have 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).

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.

Safety conclusion

No new safety concerns have been raised since 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:

Table 53

Safety concern	Proposed pharmacovigilance activities (routine and additional)	Proposed risk minimisation activities (routine and additional)
Pre and post-operative oxycodone hydrochloride administration	Routine pharmacovigilance activities	Changes to CCDS/SPC completed.
Liver enzyme elevation	Routine pharmacovigilance activities	Changes to CCDS/SPC completed.
Patients with phenylketonuria	Routine pharmacovigilance activities	No risk minimisation activities required. Orodispersible SPC and PIL communicate ingredients and risk to patients with phenylketonuria.
Inborn errors of sugar metabolism	Routine pharmacovigilance activities	No risk minimisation activities required. SPC and PIL communicate ingredients and risk to patients with sugar intolerances.
Injection site reactions	Routine pharmacovigilance activities	Update to CCDS/SPC if evidence for association identified.
Respiratory depression in opioid naïve patients	Routine pharmacovigilance activities	No risk minimisation activities required. Current posology recommendations considered to be sufficient
Tooth damage and xerostomia	Routine pharmacovigilance activities	Addition of tooth caries to section 4.8 of SPC/CCDS. No risk minimisation required for tooth loss.
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 -Media surveillance - 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 -Media surveillance - 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 - Media surveillance - 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 - Media Surveillance - Restricting prescribers - Controlled drug status

Oxycodone hydrochloride medication errors	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 - Contraindications and special warnings and precautions for use - Restricting marketing authorisation conditions - Media Surveillance -- 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 - Media Surveillance - 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 - Media Surveillance - 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

OxyContin 15 mg, 30 mg, 60 mg, 120 mg and 160 mg, prolonged-release tablets have a proven chemical-pharmaceutical quality and are approvable line extensions to OxyContin 5 mg, 10 mg, 20mg, 40 mg and 80 mg prolonged-release tablets. OxyContin 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 OxyContin® (NL License RVG 27536, 22107-22110). A study was performed to compare bioavailability of the 15/30/60/120 mg prolonged-release tablet compared to OxyContin 40 mg. Pharmacokinetics of oxycodone were demonstrated to be dose linear between 15-120 mg. The mean half-life values and median t_{max} values for oxycodone were very similar for each of the treatments. Additionally bioequivalence was demonstrated for the 160 mg tablet with two 80 mg tablets and four 40 mg OxyContin tablets.

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 OxyContin 5 mg, 10 mg, 20mg, 40 mg and 80 mg prolonged-release tablets from Mundipharma Pharmaceuticals B.V. Therefore, the Board granted a marketing authorisation. OxyContin 15 mg, 30 mg, 60 mg, 120 mg and 160 mg were authorised in the Netherlands on 26 May 2010.

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

List of abbreviations

AE	Adverse Event
ASMF	Active Substance Master File
ATC	Anatomical Therapeutic Chemical classification
AUC	Area Under the Curve
BP	British Pharmacopoeia
CCDS	Company Core Data Sheet
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
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
Update of the SPC in accordance with the CCDS and the SPC guideline. Inclusion of wording with regard to intake with alcohol.	--	II	21-12-2009	2-11-2010	Approval	N
Implementation of agreed SPC/PL wording following Art 31 referral EMA/H/A-31/1232.	--	IA	12-5-2011	14-6-2011	Approval	N
Submission of a new or updated Ph. Eur. certificate of Procedure suitability: updated certificate from an already approved manufacturer.	--	IA/G	27-1-2012	7-2-2012	Approval	N
Deletion of the PP containers for OxyContin 10, 20, 40, 80 mg.	--	IA	27-1-2012	3-2-2012	Approval	N
Change in the specification parameters and/or limits of the finished product.	--	IB	2-2-2012	1-3-2012	Approval	N
Update of the safety sections of the SPC in order to be compliant with the company core data sheet update of August 2011. In addition, the texts have been adjusted according to the latest QRD-template.	--	II/G	29-10-2012	25-6-2013	Approval	N
Submission of a new or updated Ph. Eur. certificate of Procedure suitability: updated certificate from an already approved manufacturer.	--	IA/G	2-11-2012	2-12-2012	Approval	N
Following the implementation of the new Pharmacovigilance legislation (Regulation EU No 1235/2010 and Directive 2010/84/EU) the Pharma-covigilance System Master File (PSMF) is introduced.	--	IA/G	12-4-2013	12-5-2013	Approval	N