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PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Oxynorm injectie 50 mg/ml, solution for injection or infusion
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 101605

24 July 2013

Pharmacotherapeutic group:	natural opium alkaloids
ATC code:	N02AA05
Route of administration:	intravenous, subcutaneous
Therapeutic indication:	management of severe pain requiring treatment with a strong opioid; severe postoperative pain
Prescription status:	prescription only
Date of authorisation in NL:	29 November 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 injectie 50 mg/ml, solution for injection or infusion from Mundipharma Pharmaceuticals B.V. The date of authorisation was on 29 November 2010 in the Netherlands.

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

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 OxyNorm injectie 10 mg/ml, solution for injection or infusion (NL License RVG 29031) of the same MAH, registered since 16 February 2004. Rationale for the line extension is that if doses larger than 10-20 mg are required, smaller volumes can be applied. Also registered by the same MAH are OxyNorm capsules, authorised in 2002, OxyContin prolonged-release tablets, registered since 2000, and OxyNorm oral solution (5 mg/5 ml and 10 mg/ml), registered since 2003.

The marketing authorisation is granted based on article 8(3) of Directive 2001/83/EC.

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-clinical and clinical data.
The active component of Oxynorm injectie 50 mg/ml 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 OxyNorm injectie 10 mg/ml and OxyContin 5, 10, 20, 40 and 80 mg.
The MAH has not conducted any new pharmacokinetic studies with the 50 mg/ml strength. To support the application, the MAH has submitted pharmacokinetic and clinical efficacy/safety data from previously conducted studies with OxyNorm® injectie 10 mg/ml. In addition, a study on local tolerability of the 50 mg/ml strength was conducted.

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 this product type 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 or almost white, hygroscopic powder, which is freely soluble in water, sparingly soluble in ethanol, slightly soluble in chloroform and almost insoluble in ether. Oxycodone contains four chiral centres.

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 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
Reference is made to the specifications of the Ph.Eur. monograph for oxycodone hydrochloride and the additional CEP requirements. The additional requirements regard other individual related substances and particle size. The specification is acceptable in view of the route of synthesis and the various European guidelines. Certificate of analysis for three batches has been provided.

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 injectie 50 mg/ml is a clear, colourless to pale yellow, sterile solution with pH 4.5-5.5.

The solution for injection or infusion is packed in type I Ph.Eur. clear neutral glass ampoules.

The excipients are: citric acid monohydrate, sodium citrate (E331), sodium chloride, hydrochloric acid (E507), sodium hydroxide (E524), water for injections.

Pharmaceutical development
The development of the product has been described, the choice of excipients is justified and their functions explained. The aim of the development programme was to formulate an aqueous oxycodone injection 50 mg/ml qualitatively identical to the existing oxycodone injection 10 mg/ml, only differing in amount of sodium citrate (buffer system). Some new findings are a yellow colouration and the existence of an aldol dimer. The identification and qualification of this aldol dimer has been described appropriately

and the specifications proposed are acceptable. The pharmaceutical development of the product has been adequately performed.

Manufacturing process
The same manufacturing process as with the 10 mg/ml injection is followed. Oxycodone hydrochloride injection 50 mg/ml is manufactured by dissolving oxycodone hydrochloride in an aqueous pH 5 solution containing a buffer system of sodium citrate/citric acid monohydrate and the tonicity adjuster sodium chloride. If required, the solution is pH adjusted. The solution is then filtered, filled into 1 ml ampoules, sealed and terminally sterilised. For the 50 mg/ml injection sterile filtered nitrogen is used to sparge the solution during manufacture and filtration and to purge the ampoules before and after filling. The manufacturing process has been adequately validated according to relevant European guidelines. Process validation data on the product has been presented for three full-scale batches.

Microbiological attributes
The product is terminally sterilised by autoclaving. Seal integrity of the type 1 Ph.Eur. neutral glass ampoules is checked after autoclaving by either dye testing or electronic crack detection leak testing methods. Sterility and endotoxins testing are performed on every batch of finished product.

Control of excipients
The excipients comply with the Ph.Eur. except for nitrogen. These specifications are acceptable.

Quality control of drug product
The product specification includes tests for appearance, sub-visible particles, deliverable volume, clarity of the solution, pH, assay, oxycodone hydrochloride content, degradation products, sterility and endotoxins. Release and shelf-life are identical except with respect to the degradation products; all specifications are acceptable. The analytical methods have been adequately described and validated. Batch analytical data from the proposed production sites have been provided full-scale batches, demonstrating compliance with the release specification.

Stability of drug product
Stability data on the product has been provided on three full-scale batches stored at 25°C/60% RH (24 months), 30°/65% RH (24 months) and 40°C/75% RH (9 months).
The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in 1 ml type 1 Ph.Eur. clear neutral glass ampoules. Photostability of the 50 mg/ml injection has been tested according to the ICH guideline Q1B. Results remained within the specification during the whole storage period of 36 months. Based on the stability data the claimed shelf-life of 36 months was granted and that the claimed storage conditions of no special storage conditions are acceptable. Compatibility studies of Oxynorm injectie 50 mg/ml with a range of commercially available parenteral formulations of drugs likely to be co-administered in palliative care were performed. During these studies, drug assay, appearance, clarity and pH of the solutions were monitored. The concentrations to which potential co-administered drugs can be diluted are included in the SPC.

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

Single dose/Repeat dose infusion studies – local tolerance
At the doses used in the performed single dose animal studies, no indication of local injection site irritation was evident except in the two highest doses in an acute intramuscular study, using 10 mg/ml, but not at higher concentrations. In any event, the intramuscular dose is not a clinically-indicated route of administration.
At the doses used in the repeat dose studies in animals, no indication of local injection site irritation was evident using a 10 mg/ml formulation. In studies assessing 25 and 50 mg/ml formulations, no irritation was found after acute dosing or after 24 hours of infusion. At 96 hours after dosing, there was an indication of

some irritative effects; whereas there appeared to be greater local irritative effects after 14 days of continuous infusion, particularly with the iv route. Also, based on these studies, the doses can be considered the maximum dose that could be administered for each dose route to each species. The highest dose used in the continuous infusion studies in rabbits was approximately 12 mg/kg/day (they varied slightly depending upon the exact body weight of the animals in each study). The starting doses for human use as an infusion are 48 mg/day (2 mg/hr) and 7.5 mg/day for the iv and sc routes. Assuming a 70 kg reference person, this equates to 0.7 and 0.1 mg/kg/day for the iv and sc routes, respectively. Thus, the mg/kg/day doses used in the infusion studies in rabbits are approximately 17 (iv) and 120 (sc) times the starting daily human dose.
The toxicokinetic data, although of sparse design in the parenteral studies, indicate that the pattern of metabolites is similar to that found after oral dosing. That is, noroxycodone was seen at much higher concentration than oxymorphone. Local irritation at injection sites has been reported in some cases in human patients infused iv or sc with other opioids such as morphine and hydromorphone.

It was shown that intravenous and subcutaneous injection of both the 25 mg/ml and 50 mg/ml formulations of oxycodone can cause local injection site irritation in male rabbits at doses of resp. 6 mg/kg/day and 12 mg/kg/day after more than 24 h of infusion. However, significance could not be established because of the high incidence of irritation effects were also shown in controls.
The starting dose of oxycodone for human use can be as high as 0.7 mg/kg/day (or 1 mg/kg/day for bolus injections). The safety factor therefore will be less than 6 based on mg/kg exposure, which is small. Besides, higher human doses are possible when the analgesic effect is insufficient. Unknown is the effect in female rabbits. A NOAEL ('No Observed Adverse Effect Level') has not been established in rabbits for the 50 mg/ml formulation. Based on the literature reference of the applicant, local injection site irritation of the intended use of the 50 mg/ml formulation of oxycodone may be expected.

Environmental risk assessment
The product is intended as an addition to products existing on the market. It is expected that the use of the additional strength 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.

Initially, the MAH did not conduct any new pharmacokinetic nor clinical efficacy/safety studies with the 50 mg/ml strength. To support the application, the MAH submitted pharmacokinetic and clinical efficacy/safety data from previously conducted studies with OxyNorm® injectie 10 mg/ml. However, based on limited safety data on the 50 mg/ml strength which show that the strength to be marketed is associated with local toxicity reactions, the MEB requested a study on local tolerability of the 50 mg/ml strength. The results of this study, as well as the studies with the 10 mg/ml strength, are discussed below.

The submitted data from previously conducted studies with OxyNorm® injectie 10 mg/ml are:
- bioequivalence (study OXI1202)
- bioequivalence (study OXI1203)
- one pivotal efficacy study in postoperative pain (study 0XI3201)

Clinical pharmacokinetics
Study OXI1202
This was an open, single dose, four-part, randomised, crossover study comparing pharmacokinetics of OxyNorm injection solution 10 mg/ml administered as a s.c., i.v. and i.m. bolus dose with a 5 mg/5 ml oxycodone IR solution (OxyNorm IR oral liquid) in 24 healthy male volunteers after an overnight fast. 20 complete data sets were available.

Table 1. Pharmacokinetic parameters of oxycodone.

Parameter	i.v. bolus 5 mg (n = 22)	s.c. bolus 5 mg (n = 23)	i.m. bolus 5 mg (n = 23)	IR oral liquid 5 mg (n = 23)
AUCn (ng.h.ml^{-1})[a] (SDF)	109.3 (1.18)	108.5 (1.15)	107.3 (1.17)	49.9 (1.50)
$t_{½}z$ (h)[b] (SD)	3.45 (0.37)	3.61 (0.47)	3.54 (0.37)	3.32 (0.39)
AUC (ng.h.ml^{-1})[a] (SDF)	110.4 (1.19)	109.8 (1.15)	108.6 (1.17)	51.0 (1.49)
C_{max} (ng.ml^{-1})[a] (SDF)	35.29 (1.48)	25.31 (1.20)	22.89 (1.29)	10.35 (1.55)
t_{max} (h)[c] (range)	0.08 (0.03-0.25)	0.5 (0.17-1.5)	0.5 (0.08-1.5)	1 (0.5-2)

Parameter	s.c. bolus dose / i.v. bolus dose (n = 22)	i.m. bolus dose / i.v. bolus dose (n = 21)	IR oral liquid / i.v. bolus dose (n = 21)
F_{abs}n (%)[a] (90% CI)	98.1 (88.5-108.9)	97.8 (88.1-108.5)	45.2 (40.7-50.1)
F_{abs} (%)[a] (90% CI)	98.3 (88.8-108.8)	97.9 (88.4-108.3)	45.7 (41.3-50.6)
C_{max} ratio (%)[a] (90% CI)	72.4 (61.8-84.8)	65.7 (56.1-76.9)	30.0 (25.6-35.1)

The absolute bioavailability of oxycodone after oral administration was 45% and the C_{max} values were 70% lower compared with the i.v. administration.

Oxycodone s.c. and i.m. injections were bioequivalent to the i.v. injections with regard to the extent of absorption only, with absolute bioavailability of oxycodone after s.c. and i.m. administration of 98%. C_{max} values were 28% and 34% lower for the s.c. and i.m. bolus dose administration, respectively, compared with i.v. bolus dose administration and associated 90% confidence intervals were outside the 80-125% limits of acceptability for equivalence.

Study OXI1203

This was an open, single dose, four-part, randomised, crossover study comparing pharmacokinetics of OxyNorm injection solution 10 mg/ml administered as a s.c.or i.v. 5 mg bolus dose with an i.v. or s.c. infusion (10 mg/8 h) in 24 healthy male volunteers after an overnight fast. 21 complete data sets were available.

Table 2. Pharmacokinetic parameters of oxycodone.

Parameter	i.v. bolus dose 5 mg (n = 22)	s.c. bolus dose 5 mg (n = 23)	i.v. infusion 10 mg (n = 21)	s.c. infusion 10 mg (n = 23)
AUCn (ng.h.ml^{-1})[a] (SDF)	101.7 (1.22)	96.1 (1.20)	192.1 (1.19)	179.3 (1.21)
$t_{½}z$ (h)[b] (SD)	3.72 (0.56)	3.79 (0.65)	4.09 (0.72)	4.06 (0.45)
AUC (ng.h.ml^{-1})[a] (SDF)	103.9 (1.23)	97.9 (1.21)	194.0 (1.19)	181.3 (1.21)
C_{max} (ng.ml^{-1})[a] (SDF)	47.85 (1.84)	26.66 (1.34)	19.34 (1.16)	18.97 (1.21)
t_{max} (h)[c] (range)	0.03 (0.03-0.25)	0.25 (0.083-0.75)	8.00 (8-8.167)	8.153 (8-8.75)

Parameter	i.v. infusion / i.v. bolus (n = 21)	s.c. infusion / s.c. bolus (n = 23)	s.c. bolus / i.v. bolus (n = 22)	s.c. infusion / i.v. infusion (n = 21)
F_{rel}n (%)[a] (90% CI)	96.1 (92.6-99.6)	93.8 (90.4-97.2)	93.7 (90.3-97.2)	91.5 (88.2-94.8)
F_{rel} (%)[a] (90% CI)	95.1 (91.4-98.8)	93.0 (89.5-96.7)	93.4 (89.9-97.1)	91.4 (87.9-95.0)
C_{max} ratio (%)[a] (90% CI)	20.3 (17.3-23.9)	35.6 (30.3-41.9)	55.3 (47.1-65.0)	97.1 (82.7-114.2)

[a] = Geometric mean

The absolute bioavailability and associated 90% confidence intervals of the i.v. infusion vs. single i.v. bolus dose (96%) and the s.c. infusion vs. single bolus dose (94%), were within the 80-125% limits of acceptability. In addition, the dose-adjusted i.v. infusion and s.c. infusion were bioequivalent with regard to the extent of absorption, with absolute bioavailability of oxycodone of of 91%, compared to the single i.v. and s.c. bolus dose, with absolute bioavailability of oxycodone of 93%.

The mean dose-adjusted C_{max} values from the single i.v. and s.c. bolus dose was significantly higher than those from the i.v. and s.c. infusion. The C_{max} ratio and associated 90% confidence intervals for the s.c. and i.v. infusion only were within the 80-125% limits of acceptability for equivalence.

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The infusion of oxycodone, either by the i.v. or s.c. route, provided and equivalent availability of oxycodone to a bolus injection by the same route, with regard to extent of absorption. A bolus injection of oxycodone provided an equivalent availability of oxycodone when given s.c compared with i.v. with the regard to extent of absorption. Similarly, an infusion of oxycodone provided an equivalent availability of oxycodone when given s.c. compared with i.v. with regard to extent of absorption only.

Pharmacokinetic results obtained with OxyNorm injectie® 10 mg/ml can be waived to 50 mg/ml strength, based on the fact that:
- both formulations are watery solutions
- oxycodone has linear pharmacokinetics
- the qualitative composition of the two strengths is the same
- both strengths are manufactured by the same manufacturer

Clinical experience

Safety

Study OXI3201

This was a randomised, double-blind, parallel group, multicentre study to compare the tolerability, safety and efficacy of i.v. PCA oxycodone in 133 adult patients with acute postoperative pain. 64 patients were allocated to a treatment with oxycodone (10 mg/ml) and 69 to a treatment with morphine (10 mg/ml). After surgery, patients were stabilised with i.v. bolus dose (2mg) of their allocated study treatment. The minimum and maximum durations of treatment were 1.5 hours and 170.7 hours for oxycodone, and 3.6 hours and 82.9 hours for morphine. The median (range) total use of the study medication was 69.0 (12 – 336) mg in the oxycodone group and 54.0 (7 – 212) mg in the morphine group.

There were no statistically significant treatment differences in the number and percentage of patients reporting ADRs. The commonly reported ADRs were known side effects of opioid analgesics.

Four of the 64 patients (6%) in the oxycodone group and five of the 69 patients (7%) in the morphine group discontinued because of adverse events. One patient in the oxycodone group had a serious AE that the investigator considered to be related to treatment (abdominal pain caused by postoperative constipation). This occurred 17 days after the patient had stopped receiving study medication. Respiratory depression occurred in one patient in the oxycodone group and two in the morphine group (hypoventilation); these patients recovered once medication was interrupted or discontinued.

Table 4. Most common (>10%) ADRs (safety population) in the postoperative pain study OXI3201

	Number (%) of patients				P value for treatment difference
	Oxycodone (n = 64)		Morphine (n = 69)		
Nausea	32	(50)	45	(65)	0.076
Vomiting	11	(17)	6	(9)	0.143
Constipation	3	(5)	10	(14)	0.057
Pruritus	9	(14)	5	(7)	0.201

The tolerability profile of parenteral oxycodone 10 mg/ml is typical of an opioid analgesic. The most common ADRs reported during the MAH's study in postoperative patients were nausea, vomiting, constipation, and pruritus, and the tolerability of oxycodone was similar to that of morphine.

Furthermore, the clinical overview gives a summary of the tolerability of oxycodone in the published clinical studies:

Cancer pain

In a study of Kalso and Vainio (1990)[1] oxycodone and morphine were administered to 20 patients suffering from severe cancer pain. Each patient received 10 mg/ml of both morphine and oxycodone in a randomised, double-blind, crossover manner using i.v. PCA device for 48 hours. The mean consumption of morphine was 75 ± 29 mg and of oxycodone was 84 ± 30 mg. The most commonly reported side effect was sedation (12 reports for each treatment) followed by nausea (7 reports for each treatment), and constipation (8 reports for morphine and 6 for oxycodone). In the second study of Kalso (1990a), tolerability was not assessed.

In the study of Gagnon (Gagnon et al. 1999)[2] 63 advanced cancer patients received intermittent s.c. oxycodone injections after rotation from morphine, hydromorphone (s.c., p.o. or p.r.) or oral oxymorphone. 38 patients were rotated to oxycodone because of delirium, and in 13 of those patients the delirium was reversed. Another 13 of those patients remained continued with s.c. oxycodone and the other 12 patients

[1] Kalso E, Vainio A. Morphine and oxycodone hydrochloride in the management of cancer pain. Clin Pharmacol Ther 47:639-46, 1990

[2] Gagnon, Bruno; Bielech, Monique; Watanabe, Sharon; Walker, Paul; Hanson, John; Bruera, E. The use of intermittent subcutaneous injections of oxycodone for opioid rotation in patients with cancer pain. Supportive Care in Cancer vol. 7 issue 4 June 22, 1999. p. 265 - 270

underwent other opioid rotation in an attempt to improve the cognitive failure. 13 patients switched from oral oxycodone to s.c. oxycodone. The maximum oxycodone dose varied from 4.5-660 mg in 24 h s.c. and from 1 to 49 days of administration. 7 out of those 63 patients received oxycodone in a dose > 50 mg/ml. In two patients at concentrations of 50 mg/ml and 60 mg/ml of oxycodone, s.c. oxycodone administration resulted in injection site reactions. For the patient receiving 50 mg/ml, changing the injection site allowed to continue the administration, but for the patient receiving 60 mg/ml, treatment was stopped because the reaction developed into ecchymosis.

The most common AEs reported in published clinical studies for parenterally administered oxycodone are sedation, nausea, vomiting, sweating, pruritus, and respiratory depression. The incidence and severity of AEs with parenteral oxycodone were similar to those observed with other parenteral opioids (morphine, tramadol, pethidine, and buprenorphine), except for respiratory which was some higher for oxycodone.
However, only 7 patients received the dose of oxycodone > 50 mg/ml and 2 of them developed local toxicity reactions.

Conclusion
Based on very limited literature safety data, the 50 mg/ml strength is expected to cause more injection site reactions than 10 mg/ml strength. No central side effects are expected for the 50 mg/ml strength, since C_{max} is anticipated to be similar for both strengths, the maximum i.v. bolus dose is 10 mg/ml (according to SPC) and infusion is to be performed slowly (1 – 2 min).

Local tolerability study
This study was an open, multi-centre, single therapy, non-comparative study, using oxycodone hydrochloride injection 50 mg/ml delivered as a subcutaneous infusion to subjects with severe cancer pain, for up to 20 days. A total of 33 subjects were screened and enrolled in the study. The oxycodone hydrochloride injection was diluted with as small a volume as possible of sterile 0.9% saline, sterile 5% dextrose or sterile water for injection to provide the required dosage. The dosage of study medication for each subject was calculated by the Investigator based on the individual subject's previous opioid use and current analgesia requirements. The subjects' volunteered symptoms and AEs were recorded by spontaneous reporting throughout the study and at each infusion site assessment (every 24 hours and each time the infusion was re-sited).
Overall, this study did not raise any new safety concerns regarding treatment with oxycodone hydrochloride injection 50 mg/ml. The incidence of infusion site reactions was high (55%), however, the majority were mild in nature and resolved without intervention. The pattern of other AEs was consistent with the known safety profile of oxycodone hydrochloride injection, and all deaths and SAEs were caused by the subject's underlying disease.

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:

Important Potential Risks		
Oxycodone formulation	**Safety concern**	**Planned action(s)**
All oxycodone hydrochloride formulations	Pre and post-operative oxycodone hydrochloride administration	CCDS/SPCs updated. Additional pharmacovigilance activities – active monitoring.
	Liver enzyme elevation	CCDS/SPCs updated. Continue routine pharmacovigilance activities.
Oxycodone hydrochloride orodispersible tablets	Phenylketonuria	Precaution included in SPC. Continue routine pharmacovigilance activities

Oxycodone hydrochloride formulations containing sugar	Inborn errors of sugar metabolism	Precaution included in SPC. Continue routine pharmacovigilance.
Oxycodone hydrochloride parenteral	Injection site reactions	Continue routine pharmacovigilance activities.
Oxycodone prolonged-release tablets	Respiratory depression	Precaution included in SPC. Additional pharmacovigilance activities – active monitoring.
All oxycodone hydrochloride formulations	Tooth damage and xerostomia	Event of tooth caries added to CCDS/SPCs. Tooth loss and xerostomia to be actively monitored.
	Prolongation of QTc	No evidence for association of oxycodone hydrochloride and prolongation of QTc. Resumption of routine pharmacovigilance activities.
	Interaction with Gabapentin/Pregabalin	No evidence for interaction of oxycodone hydrochloride and Gabapentin/Pregabalin. Resumption of routine pharmacovigilance activities.
	Overdose	Perform routine pharmacovigilance and focused risk minimisation activities.
	Misuse/Abuse/Diversion/ Drug Assisted Crime	Perform routine pharmacovigilance and focussed risk minimisation activities.
	Off-label use	Perform routine pharmacovigilance and focused risk minimisation activities.
	Physical dependence and withdrawal	Continue routine pharmacovigilance activities.
	Medication Errors	Continue routine pharmacovigilance activities.
	Use in children and adolescents	Continue routine pharmacovigilance activities.
	Use in pregnant and lactating women	Continue routine pharmacovigilance activities.

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. The leaflet was revised in between rounds and after the last round. The findability and comprehensibility was 99.6% based on the two test rounds. The readability test has been sufficiently performed.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Oxynorm injectie 50 mg/ml, solution for injection or infusion has a proven chemical-pharmaceutical quality and is an approvable line extension to OxyNorm injectie 10 mg/ml. Oxynorm injectie is a well-known medicinal product with an established favourable efficacy and safety profile.

For this application the MAH refers to the studies conducted with OxyNorm injectie 10 mg/ml. In addition, a local tolerability study was conducted with the 50 mg/ml strength, as requested by the MEB. Overall, this study did not raise any new safety concerns regarding treatment with Oxynorm injectie 50 mg/ml.

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 has therefore granted a marketing authorisation. Oxynorm injectie 50 mg/ml, solution for injection or infusion was authorised in the Netherlands on 29 November 2010.

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

List of abbreviations

ADR	Adverse Drug Reaction
AE	Adverse Event
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
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
NOAEL	No Observed Adverse Effect Level
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
SAE	Serious Adverse Event
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
Variations related to significant modifications of the Summary of Product Characteristics due in particular to new quality, pre-clinical, clinical or pharmaco-vigilance data.	--	II	14-6-2011	12-1-2012	Approval	N
Submission of an updated Ph. Eur. certificate of suitability.	--	IA/G	27-1-2012	7-2-2012	Approval	N
Labelling variation to update the safety sections of the SPC in order to be compliant with the company core data sheet update of August 2011; update of the texts according to the latest QRD-template.	--	II	29-10-2012	25-6-2013	Approval	N
Change in shelf life from 3 to 5 years.	--	IB	18-2-2013	20-3-2013	Approval	N
Introduction of a Pharmaco-vigilance System Master File (PSMF).	--	IA/G	12-4-2013	12-5-2013	Approval	N