Medicines & Healthcare products Regulatory Agency

MHRA Regulating Medicines and Medical Devices

Public Assessment Report

UK PAR

OxyNorm 50 mg/ml, solution for injection or infusion

(Oxycodone hydrochloride)

UK Licence No: PL 16950/0155

Napp Pharmaceuticals Limited

LAY SUMMARY

OxyNorm 50 mg/ml, solution for injection or infusion

(Oxycodone hydrochloride)

This is a summary of the Public Assessment Report (PAR) for OxyNorm 50 mg/ml, solution for injection or infusion (PL 16950/0155). It explains how the application for OxyNorm 50 mg/ml, solution for injection or infusion was assessed and its authorisation recommended, as well as the conditions of use. It is not intended to provide practical advice on how to use OxyNorm 50 mg/ml, solution for injection or infusion.

For practical information about using OxyNorm 50 mg/ml, solution for injection or infusion, patients should read the package leaflet or contact their doctor or pharmacist.

The product may be referred to as 'OxyNorm injection' or 'OxyNorm 50 mg/ml injection' in this report.

What is OxyNorm injection and what is it used for?
OxyNorm 50 mg/ml injection is used for the treatment of moderate to severe pain.

How does OxyNorm injection work?
OxyNorm injection contains the active substance oxycodone (as oxycodone hydrochloride), which belongs to a group of medicines called pain-killers (or analgesics).

How is OxyNorm injection used?
OxyNorm 50 mg/ml injection is available as a solution for injection or infusion. OxyNorm injection will usually be prepared and administered by a health professional by injection or infusion into a vein or under the skin. The injection should be used immediately after opening.

The dose and how often the injection is given may be adjusted according to the severity of the patient's pain.

Adults (over 18 years of age)
The usual starting dose is dependent upon how the injection is given - the patient's doctor will work this out.

The dose recommended by the doctor should not be exceeded.

The patient should check with the doctor or pharmacist if the patient is unsure.

Children
Children and adolescents under 18 years of age should not be given OxyNorm injection.

Please read section 3 of the package leaflet for detailed information on dosing recommendations, the route of administration, the duration of treatment and the need for any specific monitoring of certain parameters or for diagnostic tests.

OxyNorm injection can only be obtained on prescription.

What benefits of OxyNorm injection have been shown in studies?

The Marketing Authorisation Holder (MAH; Napp Pharmaceuticals Limited) provided its own data on efficacy and safety studies.

These studies have shown that OxyNorm injection is effective in treating moderate to severe pain when administered in a vein or under the skin as an injection or a continuous infusion.

What are the possible side effects of OxyNorm injection?

Like all medicines, OxyNorm injection can cause side effects although not everybody gets them.

Very common side effects
(May affect more than 1 in 10 people)
- constipation (the patient's doctor can prescribe a laxative to overcome this problem)
- feeling or being sick (this should normally wear off after a few days, however the patient's doctor can prescribe an anti-sickness medicine if it continues to be a problem)
- drowsiness (This is most likely when the patient starts taking the medicine or when the dose of Oxynorm injection is increased, but it should wear off after a few days.)
- dizziness
- headache
- itchy skin.

Common side effects
(May affect up to 1 in 10 people)
- dry mouth, loss of appetite, indigestion, abdominal pain or discomfort, diarrhoea
- confusion, depression, a feeling of unusual weakness, shaking, lack of energy, tiredness, anxiety, nervousness, difficulty in sleeping, abnormal thoughts or dreams
- difficulty in breathing or wheezing, shortness of breath, decreased cough reflex
- rash
- sweating.

For the full list of all side effects reported with OxyNorm injection, see section 4 of the package leaflet.

For the full list of restrictions, see the package leaflet for OxyNorm injection.

Why is OxyNorm injection approved?

It was concluded that, in accordance with EU requirements that, for OxyNorm injection, the benefits outweigh the identified risks and it was recommended that it be approved for use.

What measures are being taken to ensure the safe and effective use of OxyNorm injection?

Safety information has been included in the Summary of Product Characteristics and the package leaflet for OxyNorm injection, including the appropriate precautions to be followed by healthcare professionals and patients.

Other information about OxyNorm injection

A Marketing Authorisation was granted in the UK to Napp Pharmaceuticals Limited on 14 January 2009.

The full PAR approved for OxyNorm injection follows this summary.

For more information about treatment with OxyNorm injection, read the package leaflet, or contact your doctor or pharmacist.

This summary was last updated in August 2016.

SCIENTIFIC DISCUSSION

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Scientific discussion

I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the MHRA granted Napp Pharmaceuticals Limited a Marketing Authorisation for the medicinal product OxyNorm 50mg/ml Concentrate for Solution for Infusion (PL 16950/0155) on 14 January 2009. The product is a prescription only medicine (POM) indicated for the treatment of:

- moderate to severe pain in patients with cancer and post-operative pain
- severe pain requiring the use of a strong opioid.

The application was submitted as an abridged national application, according to Article 8.3(i) of Directive 2001/83/EC, as amended. The application refers to the existing Marketing Authorisation, OxyNorm 10mg/ml Infusion (PL 16950/0128), licensed to the same Marketing Authorisation Holder on 14 April 2003.

The drug product is a solution for injection or infusion containing 50mg/ml of the active ingredient oxycodone hydrochloride. This product is indicated for the treatment of moderate to severe pain in patients with cancer and post-operative pain.

Oxycodone is a full opioid agonist with no antagonist properties.

II QUALITY ASPECTS

II.1 Introduction

Each ml of solution for injection or infusion contains 50 mg of oxycodone hydrochloride (equivalent to 45 mg of oxycodone) as the active ingredient. Other ingredients consist of pharmaceutical excipients, namely citric acid monohydrate, sodium citrate, sodium chloride, dilute hydrochloric acid, sodium hydroxide and water for injections. Appropriate justification for the inclusion of each excipient has been provided.

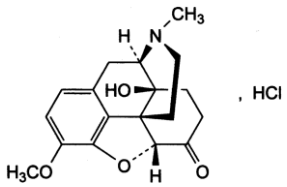
The finished product is distributed in clear 1ml glass (type I) ampoules and packaged in cartons of 5 ampoules.

II.2 DRUG SUBSTANCE

Oxycodone Hydrochloride

INN: Oxycodone hydrochloride

Structure:



Molecular formula: $C_{18}H_{22}ClNO_4$

Molecular weight: 351.9

Physical form: White crystalline powder

Solubility: Freely soluble in water, sparingly soluble in anhydrous ethanol, practically insoluble in toluene

All aspects of the manufacture, in-process controls, validation and active substance specification are covered by a certificate of suitability; in addition tests for, related substances and particle size are conducted by the drug substance manufacturer.

Oxycodone hydrochloride is a subject of a monograph in European Pharmacopoeia. The specification for the active substance as tested by the finished product manufacturer has been provided.

Active oxycodone hydrochloride is stored in a low-density polyethylene bag inside an aluminium tin, a polypropylene drum or a high-density drum.

Batch analyses data are provided and comply with the proposed specification.

The retest period for the drug substance is stated on the certificate of suitability to be 5 years when in the appropriate packaging. No further stability data has been provided, which is acceptable, as this would have been assessed in relation to the granting of the Certificate of Suitability.

II.3 MEDICINAL PRODUCT

Pharmaceutical Development

All excipients used comply with their respective European Pharmacopoeial monograph. Satisfactory Certificates of Analysis have been provided for all excipients.

None of the excipients used contains material of animal or human origin.

There were no novel excipients used and no overages.

Impurity Profiles

Impurity profiles for the drug product were found to be similar to that of the currently marketed 10mg/ml strength.

Manufacturing Process

A description and flow-chart of the manufacturing method has been provided.

In-process controls are appropriate considering the nature of the product and the method of manufacture. Satisfactory process validation data have been provided on three commercial scale batches. All data are within specifications.

Control of Finished Product

The finished product specification is satisfactory. Acceptance limits have been justified with respect to conventional pharmaceutical requirements and, where appropriate, safety. Test methods have been described and have been adequately validated, as appropriate. Batch data have been provided and comply with the release specification. Certificates of analysis have been provided for any working standards used.

Stability of the Product

Finished product stability studies have been conducted in accordance with current guidelines. Based on the results, a shelf-life of 36 months unopened has been set, which is satisfactory. Storage conditions are "After opening use immediately". For further information on use after opening see Section 6.6 of the SmPC, or the section on "Instructions for use /handling" in the leaflet for Health Professionals.

II.4 Discussion on chemical, pharmaceutical and biological aspects

It is recommended that a Marketing Authorisation is granted for this application.

III NON-CLINICAL ASPECTS

The application was submitted as a national, abridged, complex application, according to Article 8.3(i) of Directive 2001/83/EC, as amended.

There are no clinically significant toxicological issues reported in the literature for oxycodone preparations. A non-clinical expert report has been written by an adequately qualified person and is satisfactory.

It is recommended that a Marketing Authorisation is granted for this application, from a non-clinical point of view.

IV. CLINICAL ASPECTS

IV.1 Introduction.

The application is a full application made under Article 8.3(i).

This is a complex application for OxyNorm solution for injection or infusion 50 mg/ml.

The proposed product is a line extension of an authorised medicinal product. The application is for a fundamental change (addition of a new strength) to the existing product licence as referred to I Annex II of EC regulations No1084/2003 or 1085/2003 as amended.

A line extension has been proposed to extend the flexibility of administration of the product when used in syringe drivers by increasing the oxycodone hydrochloride concentration to 50 mg / ml in 1 ml glass ampoules, thereby reducing the volume in the syringe driver, which is particularly important if dose requirements increase. In this way, the possibility of coadministration with other parenteral products may be more readily achieved in the same syringe driver, where necessary, assuming no incompatibility issues exist. This new concentration of oxycodone hydrochloride injection is intended for the management of severe pain which requires opioid treatment.

A clinical overview has been written by an adequately qualified person. The clinical overview is acceptable.

IV.2 Pharmacokinetics

Two single dose pharmacokinetic studies using 10 mg / ml oxycodone hydrochloride injection have been performed by the applicant, in accordance with CPMP/EWP/280/96.

OXI1202 was conducted as an open, single dose, four-part, crossover study in 24 healthy, male volunteers. Each subject was randomised to the four treatments and then crossed over to compare the pharmacokinetics of oxycodone from oxycodone injection 10 mg / ml administered subcutaneously, intravenously or intramuscularly, or Oxycodone liquid 5 mg / 5ml administered orally. Twenty-one subjects completed all four study periods, however, due to a failed cannula during one i.v. injection, only 20 complete sets of data were available.

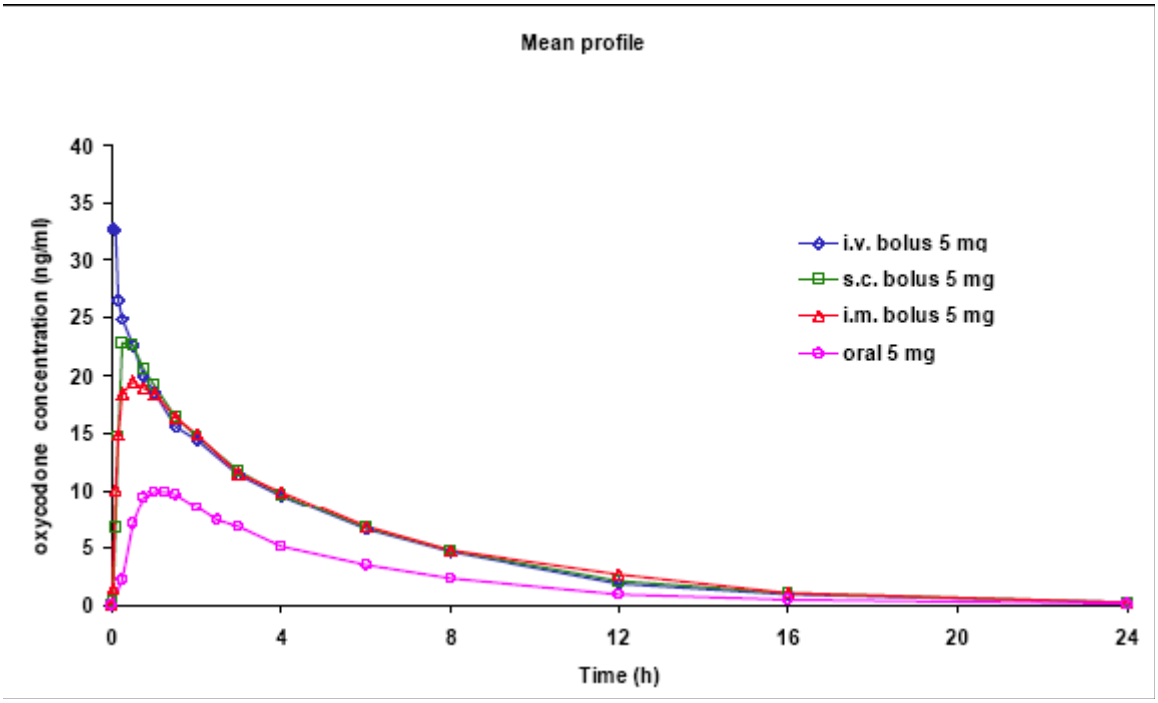
During each study period, 7 ml blood samples were taken before dosing and then at the following times after dosing for the analysis of oxycodone, noroxycodone and oxymorphone concentrations:
• Oxycodone injection 10 mg / ml (i.v., s.c. or i.m. bolus dose) -
2, 5, 10, 15, 30, 45 min and then 1, 1.5, 2, 3, 4, 6, 8, 12, 16 and 24 hours
• Oxycodone IR liquid 5 mg / 5 ml (single oral dose) -
15, 30, 45 min and then 1, 1.25, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 16 and 24 hours

The data were used to characterise the pharmacokinetic parameters of AUCn, AUC, Fabsn, Fabs, C_{max} $t_{max.}$ λz and t1/2z.

A large proportion of the plasma samples contained levels of oxymorphone that were below the limit of quantification for the oxymorphone assay. It was therefore not possible to carry out pharmacokinetic analysis on these data.

The 90% confidence intervals associated with the absolute bioavailability of oxycodone and noroxycodone for s.c. and i.m. administration were within the 80 -125% limits of acceptability for bioequivalence. The oxycodone oral liquid had a reduced mean availability (Fabs) of oxycodone compared with the i.v. bolus dose (46%).

As anticipated, the oxycodone C_{max} values for s.c. and i.m. administration were lower than for i.v. administration. In addition, oxycodone oral liquid had a significantly lower C_{max} than i.v. administration and C_{max} for noroxycodone was significantly higher (Figures 2.7.2.2.1).



The results demonstrate that the single sub cutaneous injection and the single intramuscular injection provided an equivalent availability to the single intravenous injection.

Study OXI1203 was an open, randomised, four-part, crossover study in 24 healthy, male volunteers. The pharmacokinetics of oxycodone were compared for 0.5 ml oxycodone injection 10 mg / ml as a single i.v. and s.c. bolus dose of 5 mg and oxycodone injection 10 mg / ml as an i.v. and s.c. infusion of 10 mg over 8 hours (1.25 mg / hour). Twenty-one of the 24 subjects completed all four study periods: One subject's data was excluded from the analysis because the data did not form a complete profile characterised over the time stipulated in the protocol. During each study period, blood samples were taken before dosing and then at the following times after dosing for the analysis of oxycodone, noroxycodone and oxymorphone concentrations:

• Oxycodone injection 10 mg / ml (i.v., or s.c. bolus dose) -
2, 5, 10, 15, 30, 45 min and then 1, 2, 3, 4, 6, 8, 12, 16 and 24 hours

• Oxycodone injection 10 mg / ml (i.v., or s.c. infusion) -
1, 2, 4 and 6 hours after infusion start, immediately after infusion ends and at 5, 10, 15, 30, 45 min and 1, 2, 4, 6, 8, 12, 16 and 24 hours after infusion stopped.

The data were used to characterise the pharmacokinetic parameters of AUCn, AUC, Freln, Frel, C_{max}, tmax, λz and t1/2z. The primary comparisons of interest were i.v. infusion vs single i.v. bolus dose, and s.c. infusion vs single s.c. bolus dose.

Secondary comparisons ofinterest were single s.c. bolus dose vs single i.v. bolus dose and s.c. infusion vs .v. infusion.

The i.v. and s.c. infusions provided an equivalent, dose-adjusted bioavailability to the i.v. and s.c. bolus doses, respectively and the different routes of administration provided an equivalent bioavailability of both oxycodone and noroxycodone.

As expected, there were significant differences, between the C_{max} values for the infusion vs. bolus doses, and the s.c. infusion vs. the s.c. bolus dose. There was also a significant difference between C_{max} values for the s.c. and i.v. bolus doses, but Cmax values for the s.c. and i.v. infusions were comparable. As expected for the infusions, the tmax values coincided with the end of the infusion. The i.v. infusion t½z value was statistically significantly longer than the value for the i.v. bolus dose.

Unlike oxycodone, the C_{max} ratios for noroxycodone were all associated with 90% confidence intervals that lay within the 80 – 125% limits accepted for equivalence. The mean ratios of the AUCn values for noroxycodone relative to oxycodone were comparable for all the parenteral routes. The values were slightly higher than those recorded in OXI1202, which is probably a consequence of inter-study variability.

The infusion of oxycodone, either by the i.v. or s.c. route, provided an equivalent availability of oxycodone to a bolus injection by the same route. A bolus injection of oxycodone provided an equivalent availability of oxycodone when given subcutaneously compared with intravenously. Similarly, an infusion of oxycodone provided an equivalent availability of oxycodone when given subcutaneously compared with intravenously. The maximum plasma concentration for the subcutaneous infusion was equivalent to the intravenous infusion.

Conclusion
Although these studies were conducted with a 10mg/ml concentration of oxcodone the results are considered applicable to the 50 mg/ml solution when given at the same dose as both are aqueous injectable solutions. The studies demonstrate that there is an equivalent availability of oxycodone when it is administered by the intravenous and subcutaneous routes as a bolus dose or as a continuous infusion over 8 hours. The data are adequate to support the proposed posology of the 50 mg/ml strength.

IV.3 Pharmacodynamics

Oxycodone belongs to the pharmacotherapeutic group: natural opium It has an affinity for kappa, mu and delta opiate receptors in the brain and spinal cord. Oxycodone is similar to morphine in its action. The therapeutic effect is mainly analgesic, anxiolytic and sedative.

Endocrine system
Opioids may influence the hypothalamic-pituitary-adrenal or –gonadal axes. Some changes that can be seen include an increase in serum prolactin, and decreases in plasma cortisol and testosterone. Clinical symptoms may be manifest from these hormonal changes.

Other pharmacological effects
In vitro and animal studies indicate various effects of natural opioids, such as morphine, on components of the immune system; the clinical significance of these findings is unknown. Whether oxycodone, a semisynthetic opioid, has immunological effects similar to morphine is unknown.

IV.4 Clinical Efficacy
No formal efficacy data derived from studies of patients have been provided for this application. The applicant refers to the clinical development program for the original product line. This is acceptable.

IV.5 Clinical Safety
No new formal safety data have been provided for this application and none are required.

IV.6 Risk Management Plan (RMP)
The requirement to submit an RMP with an initial marketing authorisation application came into effect on 21 July 2012. This application was submitted and approved prior to this date. Safety information has been included in the Summary of Product Characteristics and the package leaflet for OxyNorm 50 mg/ml injection, including the appropriate precautions to be followed by healthcare professionals and patients.

IV.7 Discussion of the clinical aspects
The data are adequate to support the addition of a 50 mg per ml strength of oxycodone solution for infusion to allow for the use of a lower volume of solution in a syringe driver.

The rationale for the addition of the new strength of oxycodone is accepted. Satisfactory evidence is available that the benefit/risk balance of oxycodone is acceptable in the proposed dose range. Approval is recommended.

V. USER CONSULTATION
User testing results have been submitted. The results indicate that the Patient Information Leaflet (PIL) is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

QUALITY
The important quality characteristics of OxyNorm 50mg/ml Solution for Injection or Infusion are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

NON-CLINICAL
No new non-clinical data were submitted and none are required for an application of this type.

EFFICACY
No new efficacy data were submitted for the applicant's OxyNorm 50mg/ml Concentrate for Solution for Injection or Infusion. The applicant refers to the clinical development program for the original product line; this is acceptable.

SAFETY
No new or unexpected safety concerns arise from this application.

PRODUCT LITERATURE

The SmPC, PIL and labelling are satisfactory and in line with current guidance.

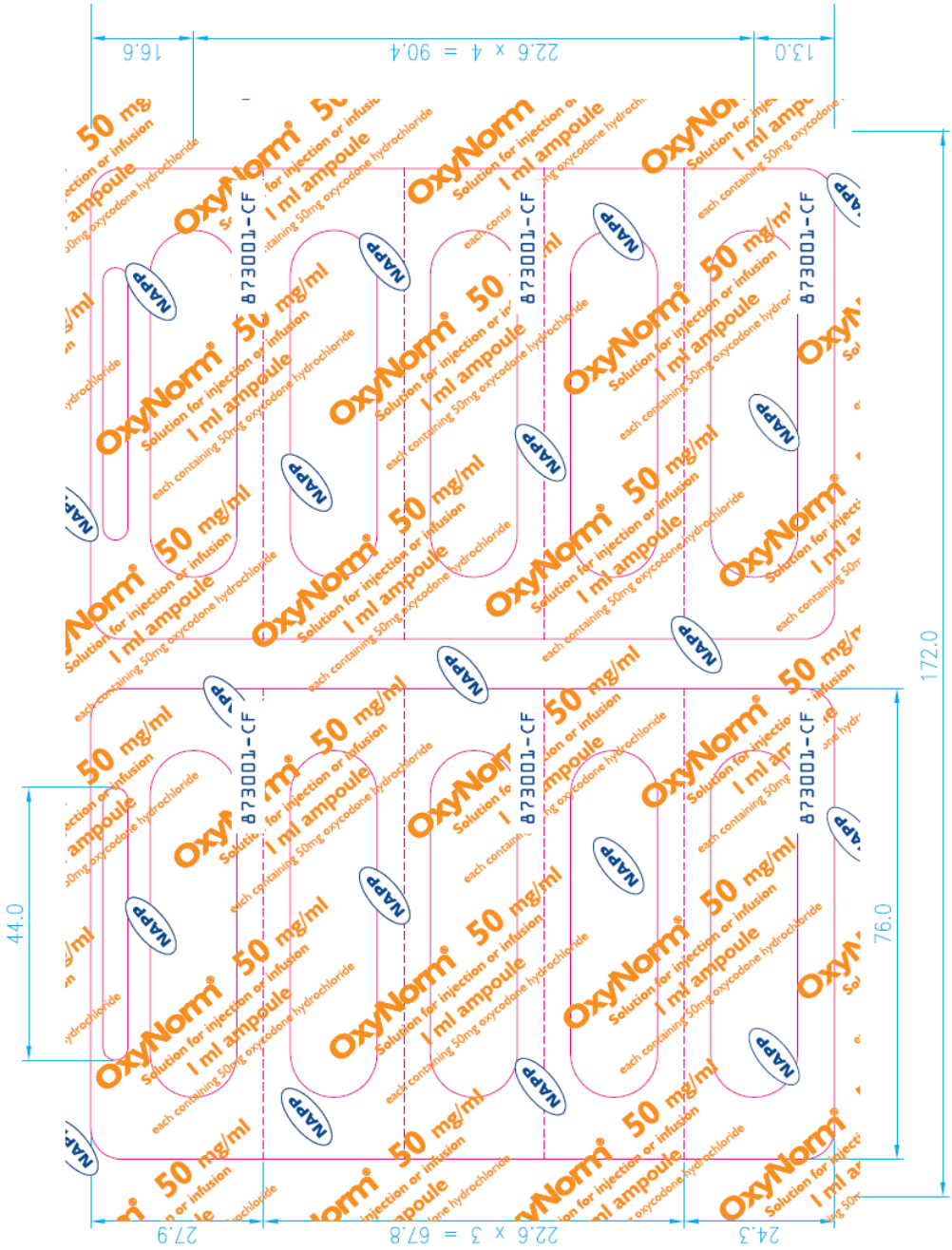
BENEFIT/RISK ASSESSMENT

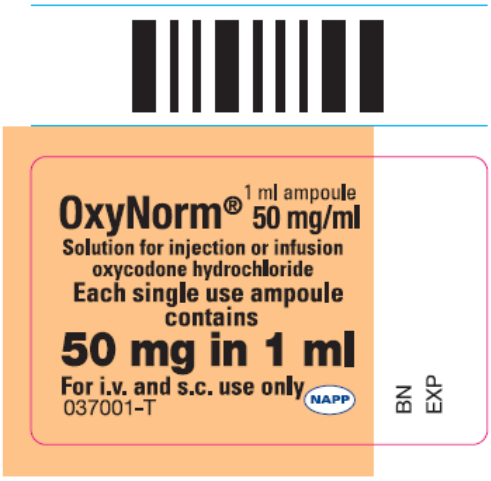
The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. Extensive clinical experience with oxycodone hydrochloride is considered to have demonstrated the therapeutic value of the active substance. The risk:benefit is, therefore, considered to be positive.

RECOMMENDATION

The grant of a Marketing Authorisation is recommended.

In accordance with Directive 2010/84/EU, the current version of the SmPC and PIL are available on the MHRA website. The current labelling is presented below:


16.6
22.6 x 4 = 90.4
13.0
172.0
44.0
76.0
27.9
22.6 x 3 = 67.8
24.3
OxyNorm
50 mg/ml
1 ml ampoule
Solution for injection or infusion
each containing 50mg oxycodone hydrochloride
037001-CF
NAPP


OxyNorm®
1 ml ampoule
50 mg/ml
Solution for injection or infusion
oxycodone hydrochloride
Each single use ampoule contains
50 mg in 1 ml
For i.v. and s.c. use only
037001-T
NAPP
BN
EXP

OXYNORM 50MG/ML, SOLUTION FOR INJECTION OR INFUSION

(Oxycodone hydrochloride)

PL 16950/0155

STEPS TAKEN AFTER AUTHORISATION-SUMMARY

The following table lists non-safety updates to the Marketing Authorisation for this product that have been approved by the MHRA since the product was first licensed. The updates have been added as annexes to this PAR. This is not a complete list of the post-authorisation changes that have been made to this Marketing Authorisation.

Date submitted	Application type	Scope	Outcome
19/11/2012	Type 1B	To increase the shelf life from 3 years unopened to 5 years unopened. Section 6.3 of the SmPC has been updated.	Approved on 23 April 2013
28 August 2015	Type II	To update Section 5.1 (Pharmacodynamics) of the Summary of Product Characteristics (SmPC) and consequently the Leaflet, in line with the Company Core Data Sheet (CCDS).	Approved on 29 June 2016

Annex 1

Our Reference: PL 16950/0155, Application 34
Product: OxyNorm 50 mg/ml, solution for injection or infusion
Marketing Authorisation Holder: Napp Pharmaceuticals Limited
Active Ingredient(s): Oxycodone hydrochloride

Type of Procedure: National
Submission Type: Variation
Submission Category: Type II
Submission Complexity: Standard
EU Procedure Number (if applicable):

Reason:
To update Section 5.1 (Pharmacodynamics) of the Summary of Product Characteristics (SmPC) and consequently the Leaflet, in line with the Company Core Data Sheet (CCDS).

Supporting Evidence
Update SmPC fragment as detailed in the table below and revised PIL.

PRESENT [10,11]	PROPOSED [10, 11]
5.1 Pharmacodynamic properties As present SPC including: Opioids may influence the hypothalamic-pituitary-adrenal or gonadal axes. Some changes that can be seen include an increase in serum prolactin and decreases in plasma cortisol and testosterone. Clinical symptoms may be manifest from these hormonal changes. In vitro and animal studies indicate various effects of natural opioids, such as morphine, on components of the immune system; the clinical significance of these findings is unknown. Whether oxycodone, a semisynthetic opioid, has immunological effects similar to morphine is unknown.	**5.1 Pharmacodynamic properties** As present SPC including: ***Gastrointestinal System*** ***Opioids may induce spasm of the sphincter of Oddi.*** ***Endocrine system*** Opioids may influence the hypothalamic-pituitary-adrenal or gonadal axes. Some changes that can be seen include an increase in serum prolactin and decreases in plasma cortisol and testosterone. Clinical symptoms may be manifest from these hormonal changes. ***Other pharmacological effects*** In vitro and animal studies indicate various effects of natural opioids, such as morphine, on components of the immune system; the clinical significance of these findings is unknown. Whether oxycodone, a semisynthetic opioid, has immunological effects similar to morphine is unknown.

Section 5.1 Pharmacodynamic Properties
A safety analysis and benefit risk assessment of biliary spasm concluded that there was insufficient evidence for a causal association between oxycodone and biliary spasm[10]. However, given the data from pharmacopoeias reviewed in the context of the safety analysis, addition of language regarding the occurrence of biliary spasm/ spasm of the sphincter of Oddi (with opioids in general) has been inserted into section 5.1.

Gastrointestinal System
Opioids may induce spasm of the sphincter of Oddi.

The sub-headings "Endocrine system" and "Other pharmacological effects" have been added, for consistency with the MAHs OxyContin (oxycodone) prolonged release tablets SmPCs.

Evaluation
The addition of sub-section headings to Section 5.1 of the SmP is acceptable. The addition of '….spasm of the sphincter of Oddi.' under the sub-section heading 'Gastrointestinal System' is also accepted.

A safety analysis and benefit risk assessment of biliary spasm concluded that there was insufficient evidence for a causal association between oxycodone and biliary spasm. Therefore, in view of the uncertainty in the causal relationship, the omission of '…spasm of the sphincter of Oddi.' in Section 4.8 of the SmPC is accepted. However the Marketing Authorisation Holder is requested to review any adverse effects related to biliary colic/spasm etcetera on a regular basis, and provide updates as necessary.

The proposed changes to the PIL are considered satisfactory.

Conclusion
The changes to the SmPC and PIL are acceptable.

Decision
Approved on 29 June 2016.