Medicines & Healthcare products Regulatory Agency

MHRA Regulating Medicines and Medical Devices

Public Assessment Report

UK PAR

OxyContin 15 mg prolonged release tablets
OxyContin 30 mg prolonged release tablets
OxyContin 60 mg prolonged release tablets
OxyContin 120 mg prolonged release tablets

(oxycodone hydrochloride)

PL 16950/0139
PL 16950/0140
PL 16950/0141
PL 16950/0150

Napp Pharmaceuticals Limited

LAY SUMMARY

OxyContin 15 mg prolonged release tablets
OxyContin 30 mg prolonged release tablets
OxyContin 60 mg prolonged release tablets
OxyContin 120 mg prolonged release tablets

(oxycodone hydrochloride)

This is a summary of the Public Assessment Report (PAR) for *OxyContin* 15 mg, 30 mg, 60 mg and 120 mg prolonged release tablets (PL 16950/0139-141 and 0150, respectively). It explains how the applications for *OxyContin* 15 mg, 30 mg, 60 mg and 120 mg prolonged release tablets were assessed and their authorisations recommended, as well as the conditions of use. It is not intended to provide practical advice on how to use *OxyContin* 15 mg, 30 mg, 60 mg and 120 mg prolonged release tablets. For practical information about using OxyContin 15 mg, 30 mg, 60 mg and 120 mg prolonged release tablets, patients should read the package leaflet or contact their doctor or pharmacist.

The products may be referred to as '*OxyContin* prolonged release tablets' in this Lay summary.

What are *OxyContin* prolonged release tablets and what are they used for?

OxyContin prolonged release tablets are used to relieve moderate to severe pain over a period of 12 hours.

How do *OxyContin* prolonged release tablets work?

OxyContin prolonged release tablets contain the active ingredient, oxycodone hydrochloride, which belongs to a group of medicines called strong analgesics or 'painkillers'.

How are *OxyContin* prolonged release tablets used?

OxyContin prolonged release tablets are taken by mouth; the tablets should be swallowed whole with water. **The tablets should not be crushed, dissolved or chewed.**

The tablets should always be taken exactly as advised by the doctor. The label on the medicine will inform the patient about how many tablets to take and how often.

Adults (over 18 years of age)

The usual starting dose is one 10 mg tablet every 12 hours. However, the patient's doctor will prescribe the dose required to treat the patient's pain. If the patient finds that he/she is still in pain whilst taking these tablets, he/she should discuss this with his/her doctor.

***OxyContin* prolonged release tablets are designed to work properly over 12 hours when swallowed whole. If a tablet is broken, crushed, dissolved or chewed, the entire 12-hour dose may be absorbed rapidly in the body. This can be dangerous, causing serious problems such as an overdose, which may be fatal.**

The tablets should never be injected as this may lead to serious side effects, which may be fatal.

Children

Children and adolescents under 18 years of age should not take the tablets.

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.

OxyContin prolonged release tablets can only be obtained with a prescription.

What benefits of *OxyContin* prolonged release tablets have been shown in studies?

The company, Napp Laboratories Limited, provided its own data from efficacy and safety studies. These studies have shown that *OxyContin* prolonged release tablets are effective in the proposed indication to relieve moderate to severe pain over a period of 12 hours in cancer pain and post-operative pain, and also for severe pain requiring the use of a strong painkiller.

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What are possible side effects of *OxyContin* prolonged release tablets?

Like all medicines, *OxyContin* prolonged release tablets can cause side effects although not everybody gets them.

As with all strong pain killers, there is a risk that the patient may become addicted or reliant on these tablets.

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 doctor can prescribe an anti-sickness medicine if it continues to be a problem).
- Drowsiness (this is most likely when a patient starts taking the tablets or when the dose 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 *OxyContin* prolonged release tablets, see section 4 of the package leaflet.

For the full list of restrictions, see the package leaflet.

Why are *OxyContin* prolonged release tablets approved?

The MHRA decided that the benefits of *OxyContin* prolonged release tablets are greater than their risks and recommended that the tablets be approved for use.

What measures are being taken to ensure the safe and effective use of *OxyContin* prolonged release tablets?

Safety information has been included in the Summary of Product Characteristics and the package leaflet for *OxyContin* prolonged release tablets, including the appropriate precautions to be followed by healthcare professionals and patients.

Known side effects are continuously monitored. Furthermore new safety signals reported by patients/healthcare professionals will be monitored/reviewed continuously.

Other information about *OxyContin* prolonged release tablets

Marketing Authorisations were granted in the UK for *OxyContin* prolonged release tablets to Napp Pharmaceuticals Limited on 07 September 2010.

The full PAR for *OxyContin* prolonged release tablets follows this summary.

For more information about treatment with *OxyContin* prolonged release tablets read the package leaflets, or contact your doctor or pharmacist.

This summary was last updated in March 2016.

SCIENTIFIC DISCUSSION

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Scientific discussion

I INTRODUCTION

The Medicines and Healthcare products Regulatory Agency (MHRA) granted Napp Pharmaceuticals Limited Marketing Authorisations for the medicinal products *OxyContin* 15 mg, 30 mg, 60 mg and 120 mg prolonged release tablets (PL 16950/0139-0141 and 0150) on 07 September 2010. These are Prescription Only Medicines (POM)

The products may be referred to as '*OxyContin* prolonged release tablets' in this report.

OxyContin prolonged release tablets are indicated for the treatment of moderate to severe pain in patients with cancer and post operative pain and for the treatment of severe pain requiring the use of a strong opioid.

These applications for *OxyContin* prolonged release tablets are submitted under Article 8(3) of EC Directive 2001/83, as amended. The applications are for a fundamental change (addition of a new strength) to an existing Product Licence, as referred to in Annex II of EC regulations No 1084/2003 or 1085/2003, as amended. Previously, oxycodone prolonged release tablets were available in strengths of 5 mg, 10 mg, 20 mg, 40 mg and 80 mg only from this Marketing Authorisation Holder. These applications were submitted to increase the range of strengths available for oxycodone prolonged release tablets to include 15 mg, 30 mg, 60 mg and 120 mg tablet strengths.

Oxycodone is a full opioid agonist with no antagonist properties. 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.

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.

The MHRA has been assured that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture, assembly and batch release of these products.

No new pharmacokinetic data have been submitted in support of the applications for the 15 mg and 30 mg tablet strengths, this is acceptable as there is adequate evidence to demonstrate that *OxyContin* exhibits linear pharmacokinetics in the dose range.

A single-dose, bioequivalence study was submitted to support the applications for the 60 mg and 120 mg strength tablets comparing the dose proportionality of one 60 mg strength tablet and one 120 mg strength tablet with one 40 mg strength tablet in the fasted state. The bioequivalence study was carried out in accordance with Good Clinical Practice (GCP).

With the exception of the bioequivalence study, no new non-clinical or clinical data were submitted, or required for the applications, which is acceptable given that these products are based on originator products that are already authorised.

II QUALITY ASPECTS

II.1 Introduction

These applications were submitted under Article 8.3 of Directive 2001/83/EC, as amended, as (addition of a new strength) to an existing Product Licence.

The submitted documentation concerning the proposed products is of sufficient quality and meets the current EU regulatory requirements.

The quality overall summary has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical aspects of the dossier.

OxyContin 15 mg prolonged release tablets are grey, round, convex tablets marked 'OC' on one side and '15' on the other.

OxyContin 30 mg prolonged release tablets are brown, round, convex tablets marked 'OC' on one side and '30' on the other.

OxyContin 60 mg prolonged release tablets are red, round, convex tablets marked 'OC' on one side and '60' on the other.

OxyContin 120 mg prolonged release tablets are purple, round, convex tablets marked 'OC' on one side and '120' on the other.

Each tablet contains 13.5 mg, 27 mg, 54 mg or 108 mg of the active ingredient, oxycodone, as 15 mg, 30 mg, 60 mg and 120 mg, respectively, of oxycodone hydrochloride. The tablets also contain lactose monohydrate, povidone, ammoniomethacrylate co-polymer, sorbic acid, triacetin, stearyl alcohol, talc and magnesium stearate in the tablet cores. The film coating for all tablet strengths contain hypromellose (E464), titanium dioxide (E171), iron oxide (E172) and macrogol 400. In addition, the film coating of the 30 mg, 60 mg and 120 mg tablets contain polysorbate 80 (E433).

Appropriate justification for the inclusion of each excipient has been provided.

The finished products are supplied in polyvinylchloride blister packs with aluminium foil backing, in pack sizes of 28, 56 and 112 prolonged release tablets.

Not all pack sizes may be marketed.

Satisfactory specifications and Certificates of Analysis for the primary packaging materials have been provided. All primary packaging complies with current European regulations concerning materials in contact with foodstuff.

II.2 DRUG SUBSTANCE

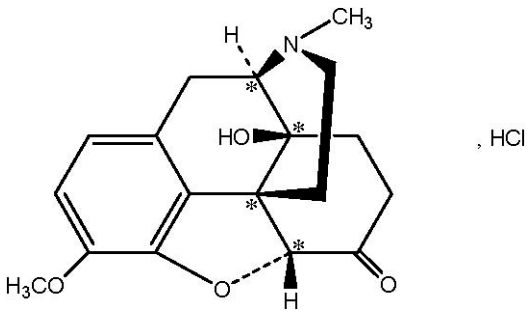
Oxycodone hydrochloride

INN:	Oxycodone hydrochloride
Chemical Name:	Morphinan-6-one, 4,5α-epoxy-14-hydroxy-3-methoxy-17-methyl-, hydrochloride 4,5-epoxy-14-hydroxy-3-methoxy-17-methyl morphinan-6-one hydrochloride 4,5-epoxy-14-hydroxy-3-methoxy-N-methyl-6-oxomorphinan hydrochloride 7,8-dihydro-14-hydroxycodeinone, hydrochloride 6-deoxy-7,8-dihydro-14-hydroxy-3-O-methyl-6-oxomorphine hydrochloride

(-)-(5R, 6S, 14S)-4,5-epoxy-14-hydroxy-3-methoxy-9a-methyl-morphinan-6-one, hydrochloride

CAS Registry Number for oxycodone hydrochloride**:** 76-42-6 oxycodone 124-90-3 oxycodone hydrochloride (anhydrous)

Structure:



Oxycodone contains four chiral centres (*)

Molecular formula:	$C_{18}H_{22}ClNO_4$ ($C_{18}H_{21}NO_4$.HCl)
M_r:	351.9
Appearance:	White or almost white powder, hygroscopic
Solubility:	Freely soluble in water, sparingly soluble in anhydrous ethanol, practically insoluble in toluene.
Isomerism	Oxycodone exhibits isomerism.

Oxycodone hydrochloride is the subject of a European Pharmacopoeia monograph.

The method of manufacture of oxycodone hydrochloride is appropriate.

The proposed drug substance specification and its justification, analytical procedures and their validation, batch analyses and reference standards used by the drug substance manufacturer are satisfactory.

Satisfactory Certificates of Analysis have been provided for working standards used by the active substance manufacturer and finished product manufacturer during validation studies.

Active oxycodone hydrochloride is stored in appropriate packaging. The specifications and typical analytical test reports are provided and are satisfactory.

Appropriate stability data have been generated supporting the retest period.

II.3 MEDICINAL PRODUCT

Pharmaceutical Development

The objective of the development programme was to formulate robust, stable, prolonged release tablets that contain 15 mg, 30 mg, 60 mg and 120 mg oxycodone hydrochloride in order to increase the range of strengths available. A satisfactory account of the pharmaceutical development has been provided.

Comparative *in vitro* dissolution profiles have been provided for the proposed and originator products.

With the exception of lactose monohydrate, none of the excipients contain materials of animal or human origin. The supplier of lactose monohydrate has confirmed that the milk used in the production of lactose monohydrate is sourced from healthy animals under the same conditions as that intended for human consumption. In addition, the supplier has confirmed that no ruminant material other than calf rennet is used during the production of lactose monohydrate.

No genetically modified organisms (GMO) have been used in the preparation of these excipients.

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. Process validation has been carried out and the results are satisfactory.

Control of Finished Product
The finished product specifications are 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 that comply with the release specifications. Certificates of Analysis have been provided for any working standards used.

Stability of the Product
Finished product stability studies were performed in accordance with current guidelines, on batches of finished product in the packaging proposed for marketing. Based on the results, a shelf-life of 3 years has been set, which is satisfactory when the storage precaution "Do not store above 25°C" is applied

Bioequivalence/Bioavailability
Satisfactory Certificates of Analysis have been provided for the test and reference batches used in the bioequivalence study.

II.4 Discussion on chemical, pharmaceutical and biological aspects

It is recommended that Marketing Authorisations are granted for these applications for *OxyContin* 15 mg, 30 mg, 60 mg and 120 mg prolonged release tablets

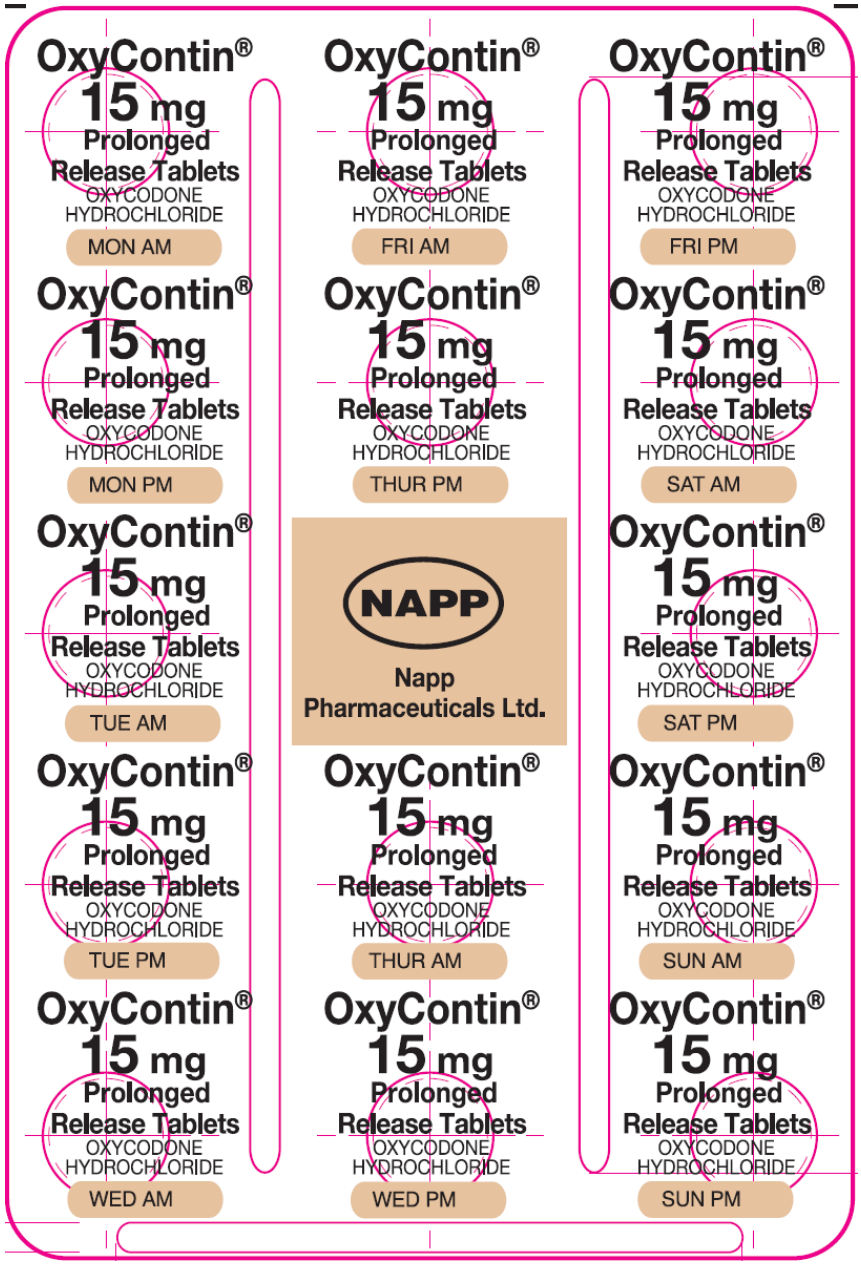
II.5 Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labels

The SmPCs, PILs and labelling are satisfactory and in line with current guidance.

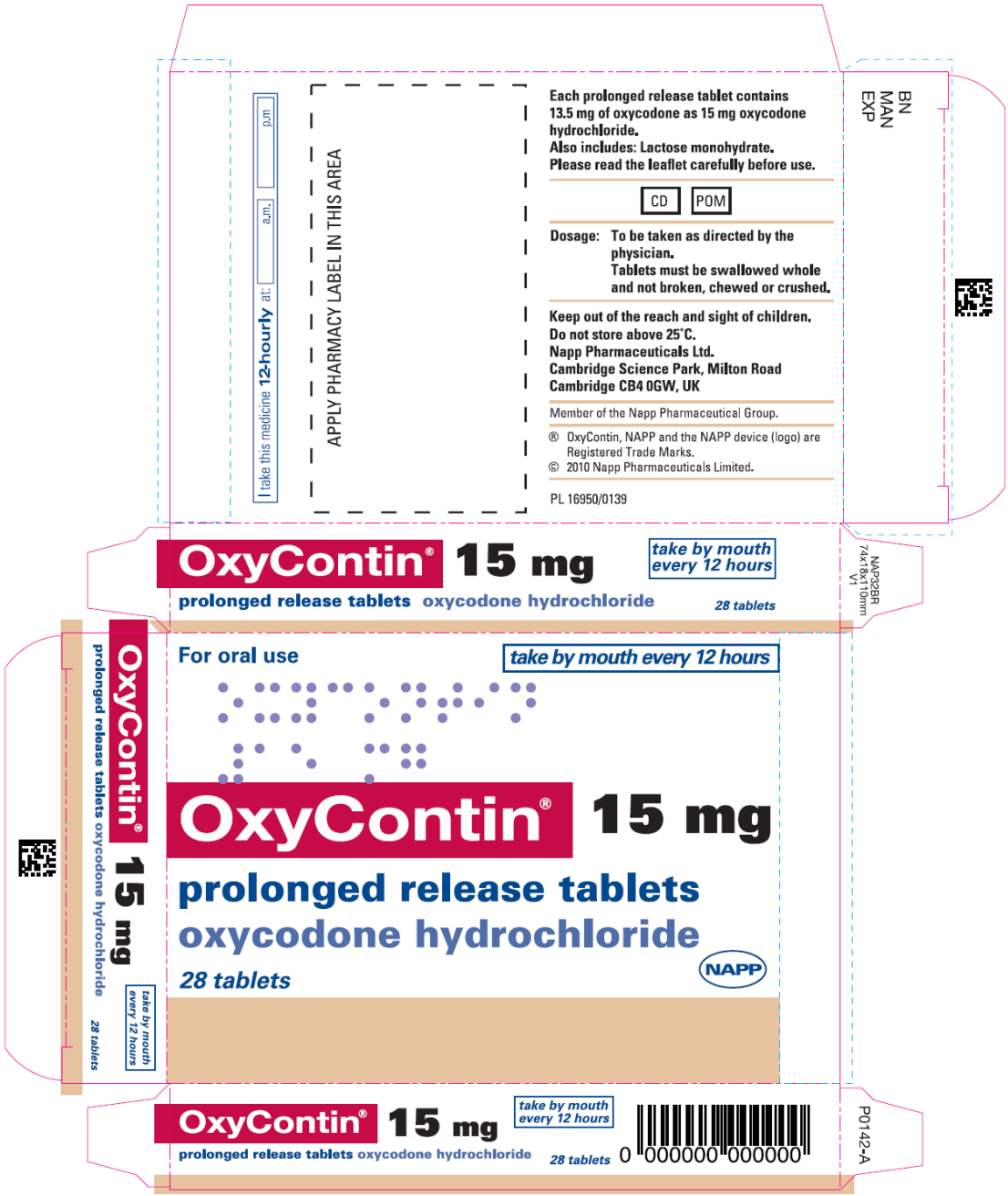
In accordance with Directive 2010/84/EU, the current version of the SmPCs and PILs is available on the MHRA website. The current labelling is presented below:

OxyContin 15 mg prolonged release tablets

Blister:



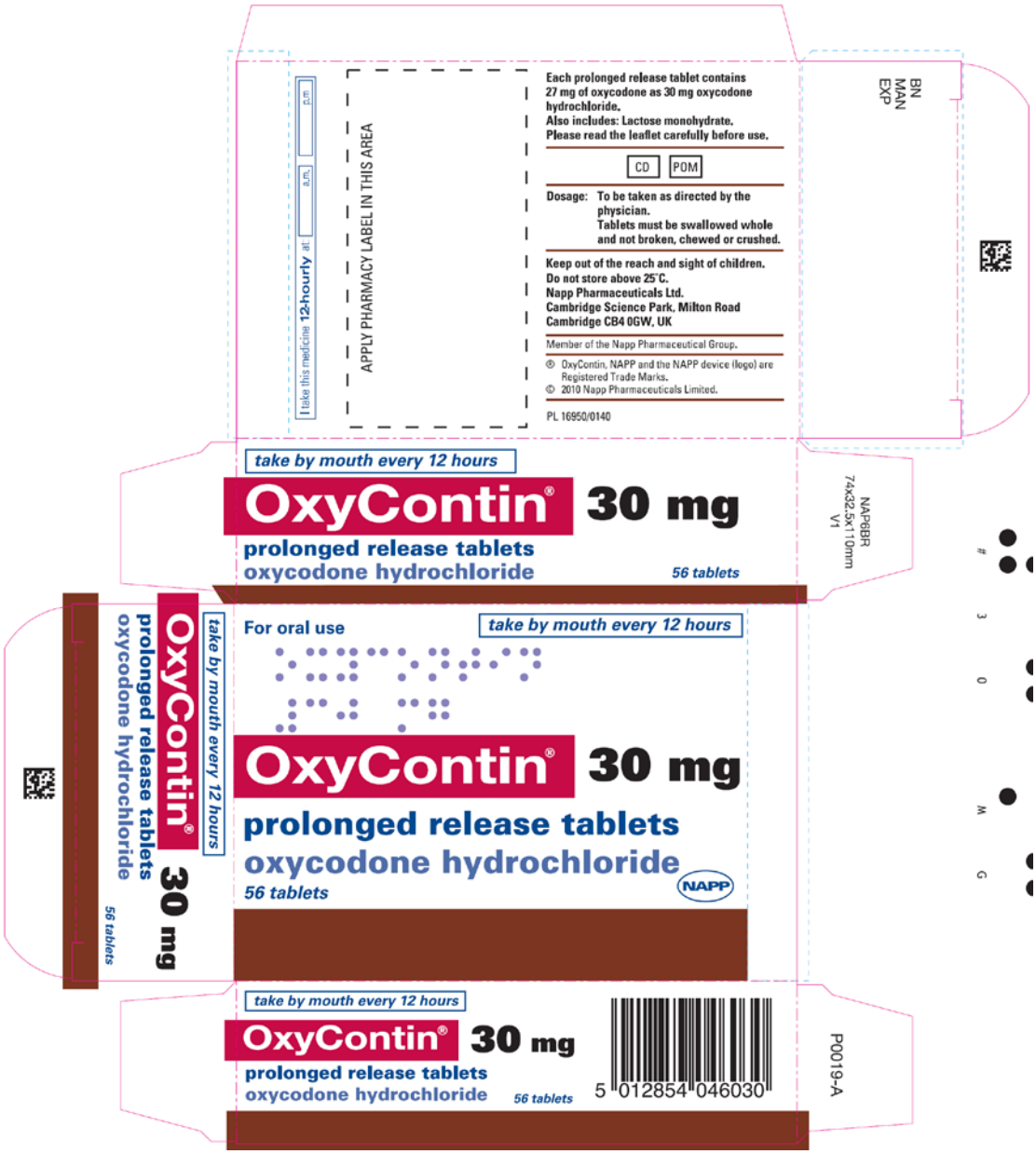
Carton:


I take this medicine 12-hourly at: a.m. p.m.
APPLY PHARMACY LABEL IN THIS AREA
Each prolonged release tablet contains 13.5 mg of oxycodone as 15 mg oxycodone hydrochloride.
Also includes: Lactose monohydrate.
Please read the leaflet carefully before use.
CD
POM
Dosage: To be taken as directed by the physician.
Tablets must be swallowed whole and not broken, chewed or crushed.
Keep out of the reach and sight of children.
Do not store above 25°C.
Napp Pharmaceuticals Ltd.
Cambridge Science Park, Milton Road
Cambridge CB4 0GW, UK
Member of the Napp Pharmaceutical Group.
® OxyContin, NAPP and the NAPP device (logo) are Registered Trade Marks.
© 2010 Napp Pharmaceuticals Limited.
PL 16950/0139
BN
MAN
EXP
OxyContin® 15 mg
take by mouth every 12 hours
prolonged release tablets oxycodone hydrochloride
28 tablets
NAP328BR
74x18x110mm
V1
For oral use
take by mouth every 12 hours
OxyContin®
15 mg
prolonged release tablets
oxycodone hydrochloride
28 tablets
NAPP
OxyContin® 15 mg
take by mouth every 12 hours
prolonged release tablets oxycodone hydrochloride
28 tablets
0 000000 000000
P0142-A

OxyContin 30 mg prolonged release tablets

Blister:

Carton:


Each prolonged release tablet contains 27 mg of oxycodone as 30 mg oxycodone hydrochloride.
Also includes: Lactose monohydrate.
Please read the leaflet carefully before use.
CD
POM
Dosage: To be taken as directed by the physician.
Tablets must be swallowed whole and not broken, chewed or crushed.
Keep out of the reach and sight of children.
Do not store above 25°C.
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Cambridge CB4 0GW, UK
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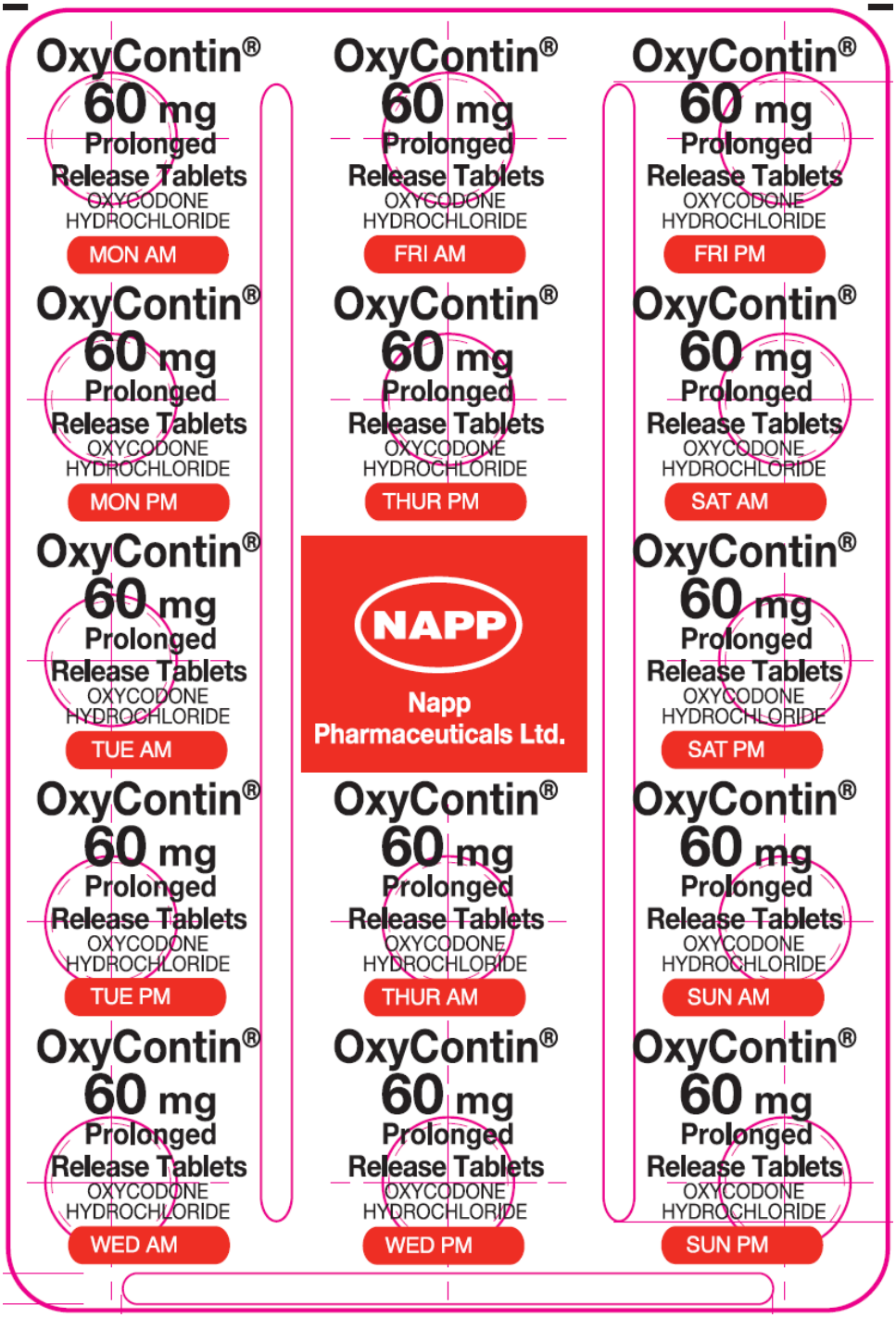
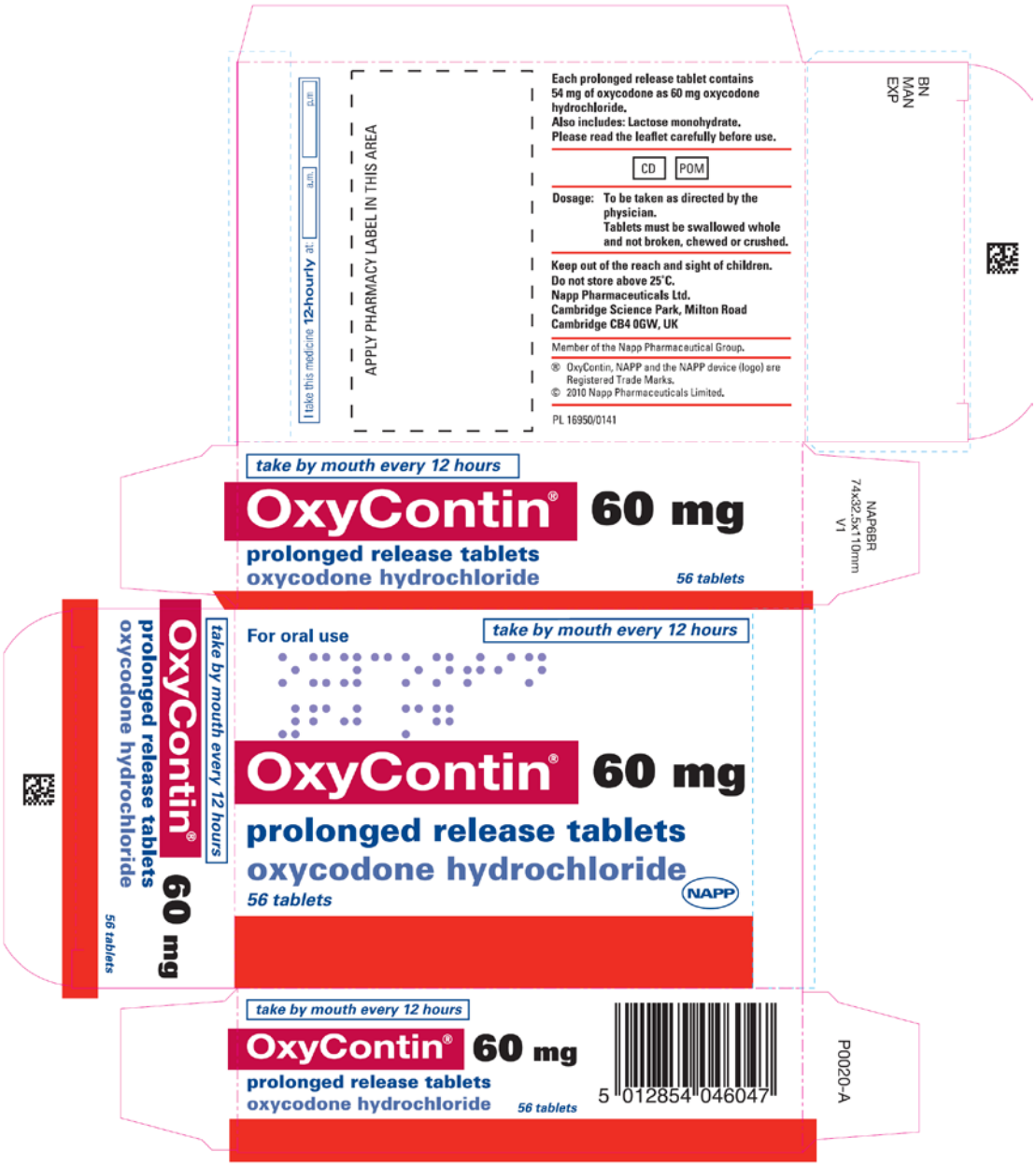
© 2010 Napp Pharmaceuticals Limited.
PL 16950/0140
APPLY PHARMACY LABEL IN THIS AREA
Take this medicine 12-hourly at: a.m. p.m.
BN
MAN
EXP
take by mouth every 12 hours
OxyContin® 30 mg
prolonged release tablets
oxycodone hydrochloride
56 tablets
NAP6BR
74x32.5x110mm
V1
For oral use
take by mouth every 12 hours
OxyContin® 30 mg
prolonged release tablets
oxycodone hydrochloride
56 tablets
NAPP
take by mouth every 12 hours
OxyContin® 30 mg
prolonged release tablets
oxycodone hydrochloride
56 tablets
5 012854 046030
P0019-A

OxyContin 60 mg prolonged release tablets

Blister



Carton:


I take this medicine 12-hourly at:
a.m.
p.m.
APPLY PHARMACY LABEL IN THIS AREA
Each prolonged release tablet contains 54 mg of oxycodone as 60 mg oxycodone hydrochloride.
Also includes: Lactose monohydrate.
Please read the leaflet carefully before use.
CD
POM
Dosage: To be taken as directed by the physician.
Tablets must be swallowed whole and not broken, chewed or crushed.
Keep out of the reach and sight of children.
Do not store above 25°C.
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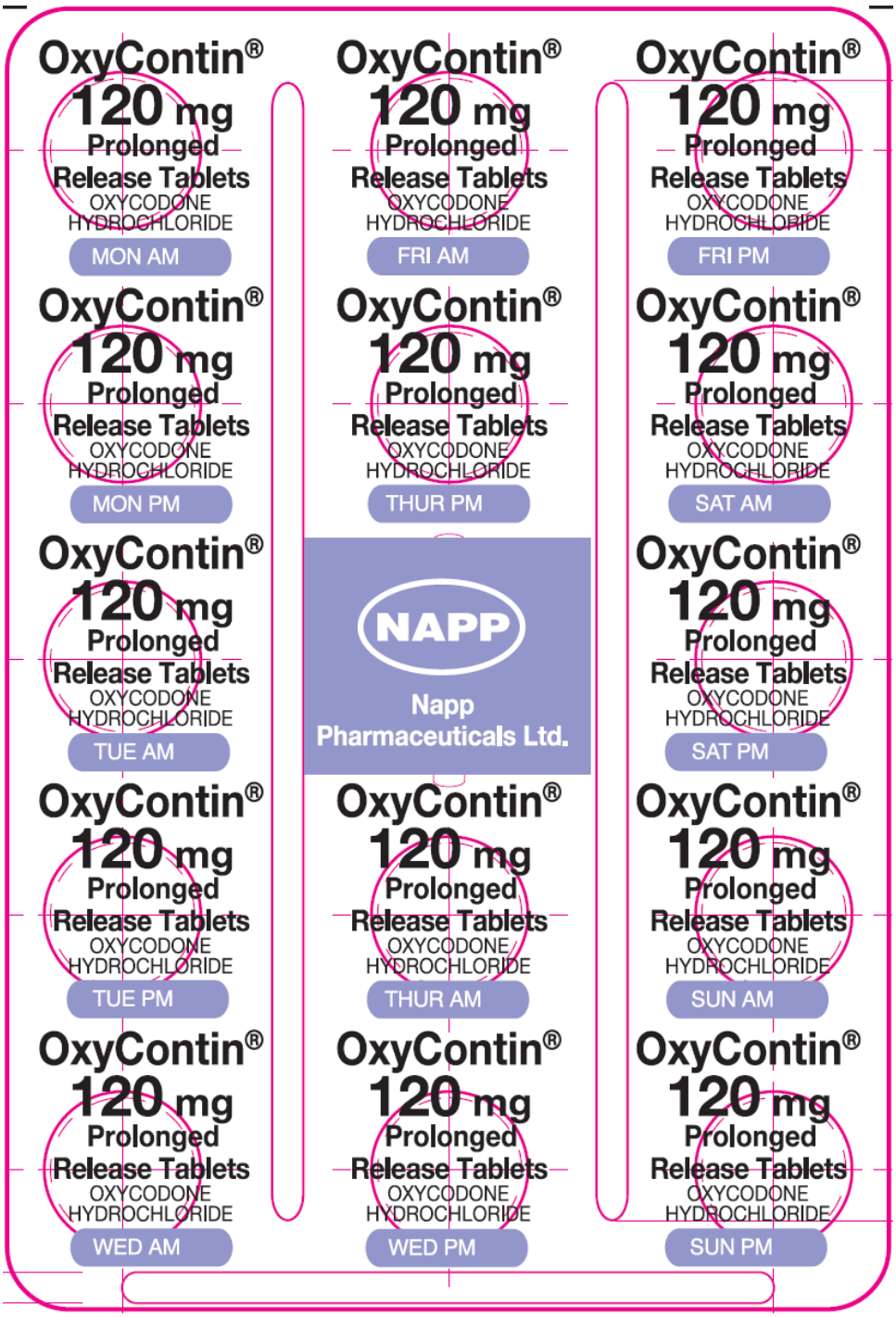
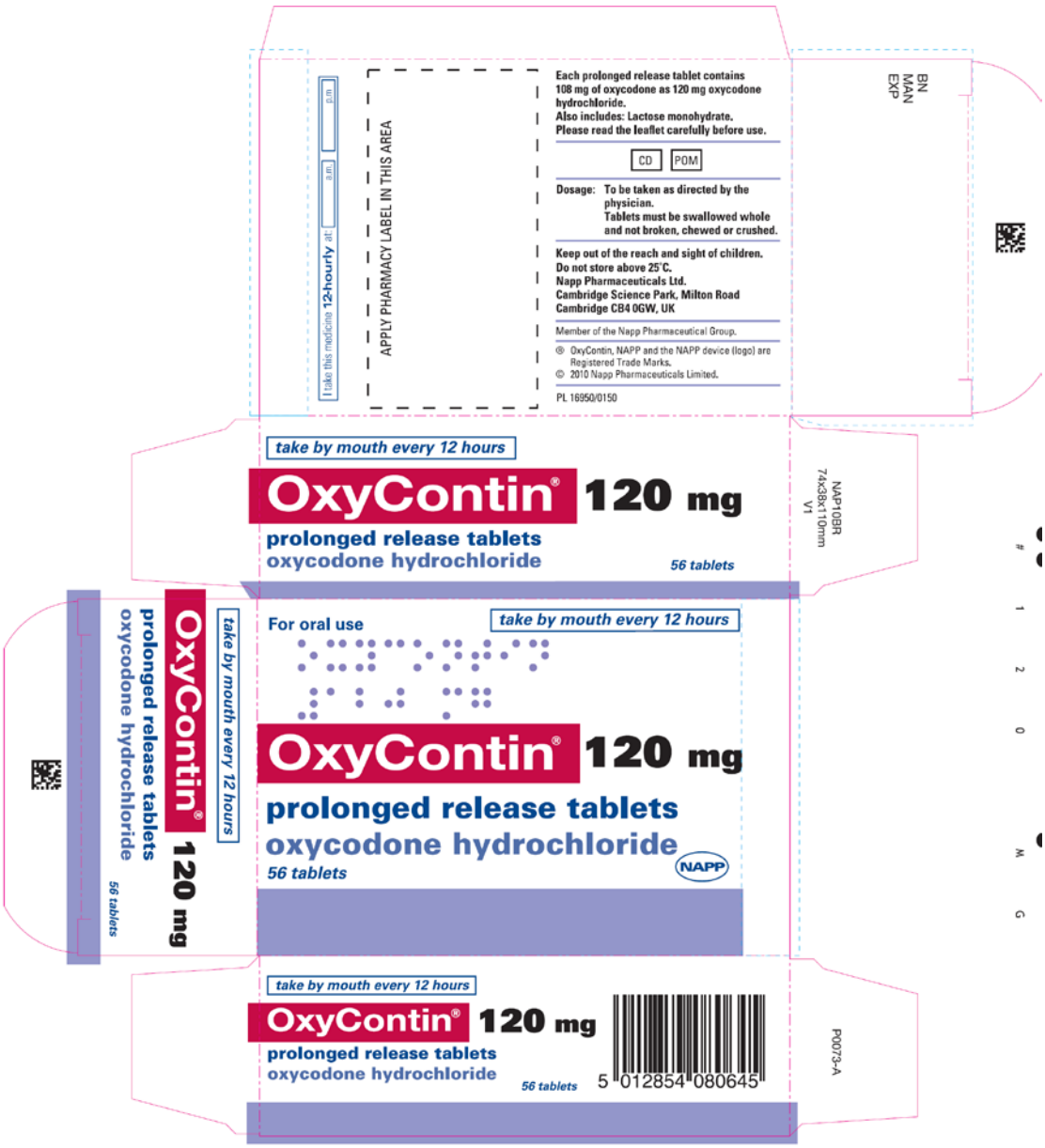
PL 16950/0141
BN
MAN
EXP
take by mouth every 12 hours
OxyContin® 60 mg
prolonged release tablets
oxycodone hydrochloride
56 tablets
NAP6BR
74x32.5x110mm
V1
For oral use
take by mouth every 12 hours
OxyContin® 60 mg
prolonged release tablets
oxycodone hydrochloride
56 tablets
NAPP
take by mouth every 12 hours
OxyContin® 60 mg
prolonged release tablets
oxycodone hydrochloride
56 tablets
5 012854 046047
P0020-A

***OxyContin* 120 mg prolonged release tablets**

Blister:



Carton:


Each prolonged release tablet contains 108 mg of oxycodone as 120 mg oxycodone hydrochloride.
Also includes: Lactose monohydrate.
Please read the leaflet carefully before use.
CD
POM
Dosage: To be taken as directed by the physician.
Tablets must be swallowed whole and not broken, chewed or crushed.
Keep out of the reach and sight of children.
Do not store above 25°C.
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® OxyContin, NAPP and the NAPP device (logo) are Registered Trade Marks.
© 2010 Napp Pharmaceuticals Limited.
PL 16950/0150
APPLY PHARMACY LABEL IN THIS AREA
I take this medicine 12-hourly at: a.m. p.m.
BN
MAN
EXP
take by mouth every 12 hours
OxyContin® 120 mg
prolonged release tablets
oxycodone hydrochloride
56 tablets
NAP10BR
74x38x110mm
V1
For oral use
take by mouth every 12 hours
OxyContin® 120 mg
prolonged release tablets
oxycodone hydrochloride
56 tablets
NAPP
take by mouth every 12 hours
OxyContin® 120 mg
prolonged release tablets
oxycodone hydrochloride
56 tablets
5 012854 080645
P0073-A

III NON-CLINICAL ASPECTS

III.1 Introduction

The pharmacodynamic, pharmacokinetic and toxicological properties of oxycodone hydrochloride are well known. No new non-clinical data have been submitted for these applications and none are required.

The applicant has provided an overview based on published literature. The non-clinical overview has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the relevant non-clinical pharmacology, pharmacokinetics and toxicology.

III.2 Pharmacology

Not applicable, see Section III.1 Introduction, above.

III.3 Pharmacokinetics

Not applicable, see Section III.1 Introduction, above.

III.4 Toxicology

Not applicable, see Section III.1 Introduction, above.

III.5 Ecotoxicity/Environmental Risk Assessment (ERA)

An ERA was not required at the time of initial assessment of these applications.

III.6 Discussion of the non-clinical aspects

It is recommended that Marketing Authorisations are granted for *OxyContin* 15 mg, 30 mg, 60 mg and 120 mg prolonged release tablets, from a non-clinical point of view.

IV. CLINICAL ASPECTS

IV.1 Introduction

The clinical pharmacology of oxycodone hydrochloride is well-known.

The applications are full applications made under Article 8(3).The proposed products are line extensions of an authorised medicinal product. The applications are for a fundamental change (addition of a new strength) to the existing Product Licence, as referred to in Annex II of EC regulations No 1084/2003 or 1085/2003, as amended.

Background

Pharmacotherapeutic group: Natural opium alkaloids
ATC code: N02A A05

Oxycodone is a full opioid agonist with no antagonist properties. 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.

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.

Indications
The following indications are proposed for these products:

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

The indications are acceptable.

Dose & dose schedule
The following Posology is proposed for these products:

"OxyContin tablets should not be taken with alcoholic drinks.

OxyContin tablets must be swallowed whole, and not broken, chewed or crushed.

Elderly and adults over 18 years:
OxyContin tablets should be taken at 12-hourly intervals. The dosage is dependent on the severity of the pain, and the patient's previous history of analgesic requirements.

OxyContin is not intended for use as a prn analgesic (i.e. as needed).

Increasing severity of pain will require an increased dosage of *OxyContin* tablets, using individual tablet strengths, either alone or in combination, to achieve pain relief. The correct dosage for any individual patient is that which controls the pain and is well tolerated for a full 12 hours. Patients should be titrated to pain relief unless unmanageable adverse drug reactions prevent this. If higher doses are necessary, increases should be made where possible, in 25% - 50% increments. The need for escape medication more than twice a day indicates that the dosage of ***OxyContin*** tablets should be increased.

The usual starting dose for opioid naïve patients or patients presenting with severe pain uncontrolled by weaker opioids is 10 mg, 12-hourly. Some patients may benefit from a starting dose of 5 mg to minimise the incidence of side effects. The dose should then be carefully titrated, as frequently as once a day if necessary, to achieve pain relief. For the majority of patients, the maximum dose is 200 mg 12-hourly.

However, a few patients may require higher doses. Doses in excess of 1000 mg daily have been recorded.

Patients receiving oral morphine before *OxyContin* therapy should have their daily dose based on the following ratio: 10 mg of oral oxycodone is equivalent to 20 mg of oral morphine. It must be emphasised that this is a guide to the dose of *OxyContin* tablets required. Inter-patient variability requires that each patient is carefully titrated to the appropriate dose.

Controlled pharmacokinetic studies in elderly patients (aged over 65 years) have shown that, compared with younger adults, the clearance of oxycodone is only slightly reduced. No untoward adverse drug reactions were seen based on age, therefore adult doses and dosage intervals are appropriate.

Children under 18 years:
OxyContin should not be used in patients under 18 years of age.

Adults with mild to moderate renal impairment and mild hepatic impairment:
The plasma concentration in this population may be increased. Therefore dose initiation should follow a conservative approach. Patients should be started on *OxyContin* tablets 5 mg 12-hourly or *OxyNorm* liquid 2.5 mg 6-hourly and titrated to pain relief as described above.

Use in non-malignant pain:
Opioids are not first-line therapy for chronic non-malignant pain, nor are they recommended as the only treatment. Types of chronic pain which have been shown to be alleviated by strong opioids include chronic osteoarthritic pain and intervertebral disc disease. The need for continued treatment in non-malignant pain should be assessed at regular intervals.

Cessation of Therapy:
When a patient no longer requires therapy with oxycodone, it may be advisable to taper the dose gradually to prevent symptoms of withdrawal."

The proposed posology is acceptable.

IV.2 Pharmacokinetics

Extensive bioequivalence studies were carried out throughout the development programme for the 10 mg, 20 mg, 40 mg and 80 mg products. The data generated confirmed that two 10 mg tablets were bioequivalent to one 20 mg tablet and that two 40 mg tablets were equivalent to one 80 mg tablet. In addition, bioequivalence was shown between one 20 mg tablet and one 40 mg tablet following dose normalisation.

15 mg and 30 mg tablets

No new pharmacokinetic data have been submitted in support of the applications for these tablet strengths, this is acceptable as there is adequate evidence to demonstrate that *OxyContin* exhibits linear pharmacokinetics in the dose range.

Table: Comparative dissolution for 30 mg and 20 mg strength batches

Strength	**30**	**30**	**30**	**20**	**20**	**20**
Hour						
1	41 (40-41)	40 (40-40)	41 (41-43)	41 (40-42)	43 (42-44)	41 (40-42)
4	71 (70-71)	70 (69-71)	72 (69-76)	71 (68-73)	74 (73-76)	72 (70-74)
12	95 (94-96)	94 (94-95)	97 (95-100)	94 (92-95)	98 (95-99)	96 (94-98)

Due to the following:

- The 15 mg and 30 mg tablets contain the same granulates as the existing 10 mg and 20 mg products, respectively.
- Dissolution profiles for the 15 mg and 30 mg strengths are comparable to those of the existing 10 mg and 20 mg products, respectively.
- The *in vitro* dissolution test is discriminatory and capable of distinguishing between batches with slow and fast product release.
- An *in vitro-in vivo* correlation has been established for the 10 mg, 20 mg, 40 mg and 80 mg strengths.
- The 15 mg and 30 mg formulations lie within the currently marketed strengths for the product range.

The absence of new bioequivalence data is clinically acceptable and a biowaiver may be granted.

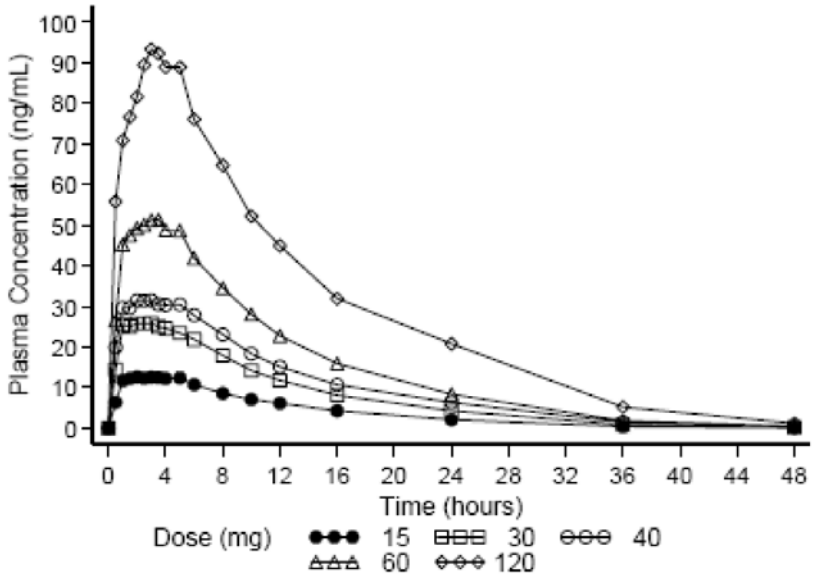
60 mg and 120 mg tablets

A single dose, randomised cross-over bioequivalence study has been performed in support of the applications for the 60 mg and 120 mg tablets. This study includes the comparison of the dose proportionality of one 60 mg strength tablet and one 120 mg strength tablet with one 40 mg strength tablet in the fasted state.

A total of 29 healthy male volunteers were recruited and blood sampling was performed to 72 hours for each of the five treatments with a 7 day washout between dosing of each treatment. In view of the doses

of *OxyContin* administered, subjects also received oral naltrexone to reduce the risk of opiod-related adverse events. The p plasma samples were analysed for oxycodone, noroxycodone, oxymorphone and noroxymorphone by a validated bioanalytical assay. All the new strengths of *OxyContin* were bioequivalent to the reference 40 mg strength in terms of AUC_t, AUC_{Inf} and C_{max} of oxycodone with respect to the administered dose. All of the bioequivalent comparisons had 90% confidence intervals that were within 80 to 125%. The mean half life values and median t_{max} values for oxycodone were very similar for each of the treatments. The mean plasma concentration-time curves are presented below for oxycodone.

Mean plasma oxycodone concentration over time
Safety population (N=29)



The incidence of adverse events (AEs) was similar across all oxycodone tablets strengths (from 15 to 120 mg). There was no apparent relationship between the incidence of AEs and oxycodone dose.

The data from this study are sufficient to demonstrate that the pharmacokinetic properties of the 60 mg and 120 mg strength tablets are proportional with those for the 40 mg strength tablets.

General Pharmacokinetics of oxycodone
Compared with morphine, which has an absolute bioavailability of approximately 30%, oxycodone has a high absolute bioavailability of up to 87% following oral administration. Oxycodone has an elimination half-life of approximately 3 hours and is metabolised principally to noroxycodone and oxymorphone. Oxymorphone has some analgesic activity but, is present in the plasma in low concentrations and is not considered to contribute to oxycodone's pharmacological effect.

The release of oxycodone from *OxyContin* tablets is biphasic with an initial relatively fast release providing an early onset of analgesia followed by a more controlled release, which determines the 12 hour duration of action. The mean apparent elimination half-life of *OxyContin* is 4.5 hours, which leads to steady-state being achieved in about one day.

Release of oxycodone from *OxyContin* tablets is independent of pH.

OxyContin tablets have an oral bioavailability comparable with conventional oral oxycodone, but the former achieve maximal plasma concentrations at about 3 hours rather than about 1 to 1.5 hours. Peak and trough concentrations of oxycodone from *OxyContin* tablets 10 mg administered 12-hourly are equivalent to those achieved from conventional oxycodone 5 mg administered 6-hourly.

OxyContin tablets 10 mg, 20 mg, 40 mg and 80 mg are bioequivalent in terms of both rate and extent of absorption. Ingestion of a standard high-fat meal does not alter the peak oxycodone concentration or the extent of oxycodone absorption from *OxyContin* tablets.

The AUC in elderly subjects is 15% greater in the elderly when compared with young subjects. Female subjects have, on average, plasma oxycodone concentrations up to 25% higher than males on a body weight adjusted basis. The reason for this difference is unknown.

Preliminary data from a study of patients with mild to moderate renal dysfunction show peak plasma oxycodone and noroxycodone concentrations approximately 50% and 20% higher, respectively and AUC values for oxycodone, noroxycodone and oxymorphone approximately 60%, 60% and 40% higher than normal subjects, respectively. There was an increase in $t_{½}$ of elimination for oxycodone of only 1 hour.

Patients with mild to moderate hepatic dysfunction showed peak plasma oxycodone and noroxycodone concentrations approximately 50% and 20% higher, respectively, than normal subjects. AUC values were approximately 95% and 75% higher, respectively. Oxymorphone peak plasma concentrations and AUC values were lower by 15% to 50%. The $t_{½}$ elimination for oxycodone increased by 2.3 hours.

IV.3 Pharmacodynamics

The clinical pharmacodynamic properties of oxycodone hydrochloride are well-known. No new pharmacodynamics data were submitted and none are required for applications of this type.

IV.4 Clinical Efficacy

No formal efficacy data derived from studies of patients have been provided for these applications. The applicant refers to the clinical development program for the original product line. This is acceptable.

IV.5 Clinical Safety

No formal safety data have been provided for these applications 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 Summaries of Product Characteristics and the package leaflet *OxyContin* 15 mg, 30 mg, 60 mg and 120 mg prolonged release tablets, including the appropriate precautions to be followed by healthcare professionals and patients.

IV.7 Discussion of the clinical aspects

OxyContin is prescribed at doses of 5 mg to 200 mg, the choice of dose is titrated against effect. The addition of 15 mg, 30 mg, 60 mg and 120 mg strengths to the range already available will allow precise dose titration with the need to administer fewer tablets and approval is recommended from a clinical point of view.

The rationale for the addition of the new strengths of *OxyContin* is accepted. Satisfactory evidence is available that the benefit risk of *OxyContin* is acceptable in the proposed dose range. Approval is recommended.

V. USER CONSULTATION

The package leaflet was submitted to the MHRA along with results of consultations with target patient groups ("user testing"), in accordance with Article 59 of Council Directive 2001/83/EC. The results indicate that the package leaflet 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 *OxyContin* 15 mg, 30 mg, 60 mg and 120 mg prolonged release tablets 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 applications of this type.

EFFICACY

The efficacy oxycodone is well established.

No new pharmacokinetic data have been submitted in support of the applications for the 15 mg and 30 mg tablet strengths, this is acceptable as there is adequate evidence to demonstrate that *OxyContin* exhibits linear pharmacokinetics in the dose range.

A single dose, randomised cross-over bioequivalence study has been performed in support of the applications for the 60 mg and 120 mg tablets. These new strengths of *OxyContin* were bioequivalent to the reference 40 mg strength in terms of AUC_t, AUC_{Inf} and C_{max} of oxycodone with respect to the administered dose. With the exception of the bioequivalence study, no new data were submitted and none are required.

SAFETY

No new safety data have been submitted with these applications. As the safety profile of oxycodone is well-known, this is satisfactory.

PRODUCT LITERATURE

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

BENEFIT/RISK ASSESSMENT

The quality of the products is acceptable, no significant preclinical or clinical safety concerns were identified, and benefit has been shown to be associated with oxycodone. The benefit/risk is therefore considered to be positive.

RECOMMENDATION

The grant of Marketing Authorisations is recommended.

OxyContin 15 mg prolonged release tablets
OxyContin 30 mg prolonged release tablets
OxyContin 60 mg prolonged release tablets
OxyContin 120 mg prolonged release tablets

(oxycodone hydrochloride)

PL 16950/0139
PL 16950/0140
PL 16950/0141
PL 16950/0150

STEPS TAKEN AFTER AUTHORISATION-SUMMARY

The following table lists a non-safety update to the Marketing Authorisations for these products that has been approved by the MHRA since the products were first licensed. The table includes an update that has been added as an annex to this PAR. This is not a complete list of the post-authorisation changes that have been made to these Marketing Authorisations.

Date submitted	Application type	Scope	Outcome
26 August 2015	Type II	To update section 5.1 of the Summaries of Product Characteristics (SmPCs/SPCs) in line with the Company Core Data Sheet. Consequently, the Patient Information Leaflet has been updated. Section 5.2 of the SmPCs has also been updated.	Approved on 29 January 2016

Annex 1

Our Reference:	PL 16950/0139 – 0026, PL 16950/0140 – 0024, PL 16950/0141 – 0024 and PL 16950/0150 - 0024
Product:	OxyContin 15 mg, 30 mg, 60 mg and 120 mg prolonged release tablets
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):	Not applicable

Reason:
To update section 5.1 of the Summaries of Product Characteristics (SmPCs/SPCs) in line with the Company Core Data Sheet. Consequently, the Patient Information Leaflet has been updated. Section 5.2 of the SmPCs has also been updated.

Supporting Evidence
Revised SmPC fragments:

PRESENT [10,11]	PROPOSED [10, 11]
5.1 Pharmacodynamic properties As present SPC	**5.1 Pharmacodynamic properties** As present SPC plus: ***Gastrointestinal System*** ***Opioids may induce spasm of the sphincter of Oddi.***

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.

PRESENT [10,11]	PROPOSED [10, 11]
5.2 Pharmacokinetic properties ***OxyContin*** tablets ***5 mg, 10 mg, 20 mg, 40 mg and 80 mg*** are bioequivalent in terms of both rate and extent of absorption. Ingestion of a standard high-fat meal does not alter the peak oxycodone concentration or the extent of oxycodone absorption from *OxyContin* tablets.	**5.2 Pharmacokinetic properties** ***All strengths of OxyContin*** tablets are bioequivalent in terms of both rate and extent of absorption. Ingestion of a standard high-fat meal does not alter the peak oxycodone concentration or the extent of oxycodone absorption from *OxyContin* tablets.

Evaluation
The proposed changes to the SmPCs and PIL are satisfactory.

Conclusion
The proposed changes to SmPCs and PIL are acceptable and there are no objections to approval.

In accordance with Directive 2010/84/EU the Summaries of Product Characteristics (SmPCs) and Patient Information Leaflets (PILs) for products granted Marketing Authorisations at a national level are available on the MHRA website.

Decision - Approved on 29 January 2016.