OXYNORM DISPERSA 5 MG ORODISPERSIBLE TABLETS
OXYNORM DISPERSA 10 MG ORODISPERSIBLE TABLETS
OXYNORM DISPERSA 20 MG ORODISPERSIBLE TABLETS

(Oxycodone hydrochloride)

PL 16950/0142
PL 16950/0143
PL 16950/0144

UKPAR

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PL 16950/0142
PL 16950/0143
PL 16950/0144

LAY SUMMARY

The MHRA granted Napp Pharmaceuticals Ltd Marketing Authorisations (licences) for the medicinal products OxyNorm Dispersa 5 mg, 10 mg and 20 mg orodispersible tablets on 18 December 2012. These products are prescription-only medicines (POM) used to relieve moderate to severe pain.

OxyNorm Dispersa 5 mg, 10 mg and 20 mg orodispersible tablets contain the active ingredient oxycodone which belongs to a group of medicines called strong analgesics or 'painkillers'.

No new or unexpected safety concerns arose from these applications and it was, therefore, judged that the benefits of taking OxyNorm Dispersa 5 mg, 10 mg and 20 mg orodispersible tablets outweigh the risks, hence Marketing Authorisations have been granted.

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OXYNORM DISPERSA 20 MG ORODISPERSIBLE TABLETS

PL 16950/0142
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SCIENTIFIC DISCUSSION

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INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the MHRA granted Napp Pharmaceuticals Ltd, Marketing Authorisations for the medicinal products OxyNorm Dispersa 5 mg, 10 mg and 20 mg orodispersible tablets (PL 16950/0142-4) on 18 December 2012. These products are prescription-only medicines (POM) 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 are applications for a known active substance submitted according to Article 8.3 of Directive 2001/83/EC as amended, as a line-extension to OxyContin 5 mg prolonged release tablets (PL 16950/0123) which was first authorised to Napp Pharmaceuticals Ltd on 21 May 2002.

Oxycodone belongs to the pharmacotherapeutic group of medicines called 'natural opium alkaloids'. 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. The therapeutic effect is mainly analgesic, anxiolytic and sedative.

No new non-clinical data have been submitted, which is acceptable given that the product is a line-extension of an approved product licence containing a well-known active substance.

One bioequivalence study (single dose) was submitted to support these applications, comparing the higher strength test product OxyNorm Dispersa 20 mg orodispersible tablets (Napp Pharmaceuticals Ltd) and the reference product Oxynorm 20mg capsules (Napp Pharmaceuticals Ltd). The bioequivalence study was carried out in accordance with Good Clinical Practice (GCP).

With the exception of the bioequivalence study, no new clinical studies were performed, which is acceptable given that the products are a line-extension of an approved product licence containing a well-known active substance.

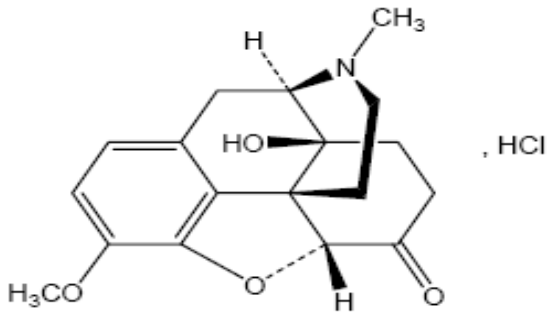
No new or unexpected safety concerns were raised during the assessment of this application and it was, therefore, judged that the benefits of taking OxyNorm Dispersa 5 mg, 10 mg and 20 mg orodispersible tablets outweigh the risks; hence Marketing Authorisations has been granted.

PHARMACEUTICAL ASSESSMENT

ACTIVE SUBSTANCE

INN: Oxycodone hydrochloride
Chemical name: 4,5α-Epoxy-14-hydroxy-3-methoxy-17-methylmorphinan-6-one hydrochloride

Structure:



Molecular formula: $C_{18}H_{22}ClNO_4$
Molecular weight: 351.9
Appearance: Oxycodone hydrochloride is a white or almost white powder.
Solubility at 20°C: Water; 1 part in 6, ethanol; 1 part in 60, chloroform; 1 part in 600.

Oxycodone hydrochloride is the subject of a European Pharmacopoeia monograph.

All aspects of the manufacture and control of the active substance oxycodone hydrochloride are covered by a European Directorate for the Quality of Medicines (EDQM) Certificate of Suitability.

MEDICINAL PRODUCT

Other ingredients

Other ingredients for all strengths of the product consist of pharmaceutical excipients, sucrose, maize starch, polyacrylate dispersion 30%, hypromellose, mannitol, silicon dioxide, microcrystalline cellulose, crospovidone, aspartame, spearmint flavour (contains maltodextrin) and magnesium stearate.

All excipients used comply with their respective European Pharmacopoeia monograph with the exception of silicon dioxide which is controlled to the United States Pharmacopeia (USP) and the National Formulary (NF) and spearmint flavour which is controlled to suitable in-house specifications. The flavouring is also in compliance with Council Directive 88/388/EEC on flavourings for use in foodstuff. Satisfactory Certificates of Analysis have been provided for all excipients.

None of the excipients contain materials of animal or human origin.

No genetically modified organisms (GMO) have been used in the preparation of this product.

Pharmaceutical development
The aim of the development programme was to formulate safe, efficacious, orodispersible tablets containing 5 mg, 10 mg or 20 mg oxycodone (as hydrochloride) to complement the existing oral, immediate release range of oxycodone hydrochloride (OxyNorm capsules 5 mg, 10 mg and 20 mg). The proposed finished product is intended to assist patients who have difficulty swallowing regular tablets or capsules.

Suitable pharmaceutical development data have been provided for these applications.

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

Satisfactory batch formula have been provided for the manufacture of the product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated at commercial scale and has shown satisfactory results. The Marketing Authorisation Holder (MAH) has also committed to perform additional process validation on future commercial scale batches for all strengths.

Finished product specification
The finished product specifications are satisfactory. 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.

Container Closure System
All strengths of the finished product are packaged in polyamide/aluminium/polyvinyl chloride (PVC) blister packs with a peelable aluminium backing foil and are available in pack sizes of 14, 28 or 56 tablets.

It has been stated that not all pack sizes may be marketed, however, the marketing authorisation holder has committed to submitting the mock-ups for any pack size to the relevant regulatory authorities for approval before marketing.

Satisfactory specifications and certificates of analysis have been provided for all packaging components. All primary packaging complies with the current European regulations concerning materials in contact with food.

Stability
Stability studies were performed in accordance with current guidelines on batches of the finished product packed in the packaging proposed for marketing. The data from these studies support a shelf-life of 36 months with no special storage conditions.

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

Summaries of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labelling
The SmPCs, PIL and labelling are satisfactory.

A package leaflet has previously been submitted to the MHRA for OxyContin 5 mg, 10 mg, 15 mg, 20 mg, 30 mg, 40 mg, 60 mg and 80 mg film-coated prolonged release tablets (PL 16950/0097-100, 0123 and 0139-0141), along with results of consultations with target patient groups ("user testing"), in accordance with Article 59 of Council Directive 2001/83/EC, as amended. 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. As the proposed PIL for OxyNorm Dispersa 5 mg, 10 mg and 20 mg orodispersible tablets (PL 16950/0142-4) is identical in layout and content to the approved PIL for OxyContin 5 mg, 10 mg, 15 mg, 20 mg, 30 mg, 40 mg, 60 mg and 80 mg film-coated prolonged release tablets (PL 16950/0097-100, 0123 and 0139-0141), additional readability testing is not deemed necessary.

Marketing Authorisation Forms (MAA)
The MAA forms are satisfactory.

Expert Report (Quality Overall Summary)
A quality overall summary has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical aspects of the dossier.

Conclusion
It is recommended that marketing authorisations are granted for these applications.

NON-CLINICAL ASSESSMENT

PHARMACODYNAMICS, PHARMACOKINETICS AND TOXICOLOGY

The pharmacological, pharmacokinetic and toxicological properties of oxycodone hydrochloride are well-known. As these products are a line-extension of an approved product licence containing a well-known active substance, no further data have been submitted and none are required. An overview based on a literature review is, thus, appropriate.

NON-CLINICAL EXPERT REPORT

The non-clinical overview has been written by an appropriately qualified person and is a suitable summary of the non-clinical aspects of the dossier.

ENVIRONMENTAL RISK ASSESSMENT

In accordance with the Committee for Medicinal Products for Human Use (CHMP), Guideline on the Environmental Risk Assessment of Medicinal Products for Human use [EMEA/CHMP/SWP/4447/00], an environmental risk assessment (ERA) has been performed. The predicted environmental concentration (PEC) in surface water for oxycodone hydrochloride (0.0026 µg /L) is below the threshold value of 0.01 µg/L; and hence no further assessment is necessary.

Based on the results of this assessment, it was concluded that the prescribed usage of oxycodone hydrochloride by patients is unlikely to pose a risk for the environment and no further action is warranted.

CONCLUSION

It is recommended that marketing authorisations are granted for these applications.

CLINICAL ASSESSMENT

CLINICAL PHARMACOLOGY

The clinical pharmacology of oxycodone hydrochloride is well-known. With the exception of the bioequivalence study, no pharmacokinetic or pharmacodynamic data were submitted for these line-extension applications, and none were required for applications of this type.

The following bioequivalence study was submitted:

An open label, randomised, two-treatment, two-sequence, single dose, crossover study to compare the pharmacokinetics of the test product OxyNorm Dispersa 20 mg orodispersible tablets (Napp Pharmaceuticals Ltd) versus the reference product Oxynorm 20mg capsules (Napp Pharmaceuticals Ltd) in healthy adult volunteers under fasted conditions.

All volunteers were administered naltrexone (an antagonist of oxycodone) approximately 2 hours prior to oxycodone administration.

All volunteers received a single oral dose of either the test or the reference product administered under fasted conditions. Blood samples were taken for the measurement of pharmacokinetic parameters at pre- and up to 24 hours post dose. The washout period between treatment periods was at least 7 days.

The pharmacokinetic results for oxycodone, for the test product versus the reference product are presented below (geometric least squares mean with ratios and 90% confidence intervals):

PARAMETER	GEOMETRIC LS MEANS		RATIO	90% CONFIDENCE INTERVAL		POWER OF STUDY (%)
	TEST	REFERENCE				
C_{max}	49.922	49.303	101.26	92.72	110.58	99
AUC_t	232.865	226.239	102.93	97.83	108.30	>99
AUC_∞	237.482	230.011	103.25	98.23	108.53	>99

AUC_t area under the plasma concentration-time curve from time zero to t hours
AUC_∞ area under the plasma concentration-time curve from time zero to infinity
C_{max} maximum plasma concentration
90% CI* 90% Geometric Confidence Interval using log-transformed data

The 90% confidence intervals for AUC and C_{max} for test versus reference product for oxycodone are within predefined acceptance criteria specified in the ”Guideline on the Investigation of Bioequivalence” (CPMP/EWP/QWP/1401/98 rev 1/, Corr**). Thus, the data show that the 20 mg orodispersible tablet test product is bioequivalent to the 20 mg capsule reference product under fasting conditions.

As the 5 mg, 10 mg and 20 mg strengths of the product meet the criteria specified in the current guideline on investigation of bioequivalence (CPMP/EWP/QWP/1401/98rev 1/Cor **), the results and conclusions of the bioequivalence study on the 20 mg strength can be extrapolated to the 5 mg and 10 mg strengths.

Pharmacodynamics
No new pharmacodynamic data were submitted and none were required for this application.

Efficacy
No new efficacy data were submitted and none were required for this application.

Safety
With the exception of the data generated during the bioequivalence study, no new safety data were submitted and none were required for these applications. No new or unexpected safety issues were raised by the bioequivalence data.

Summaries of Product Characteristics (SmPCs), Patient Information Leaflet (PIL), Labels
The SmPCs, PIL and labels are acceptable. The PIL is consistent with the SmPC and in-line with current guidelines. The labelling is in-line with current guidelines.

Clinical Expert Report
The clinical overview has been written by an appropriately qualified physician and is a suitable summary of the clinical aspects of the dossier.

Pharmacovigilance System and Risk Management Plan
The pharmacovigilance system, as described by the applicant, fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance, and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

A satisfactory Risk Management Plan has been submitted for these products.

Conclusion
There are no objections to the approval of these products from a clinical viewpoint.

IV OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

QUALITY

The important quality characteristics of OxyNorm Dispersa 5 mg, 10 mg and 20 mg orodispersible 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

With the exception of the bioequivalence study, no new data were submitted and none are required for an application of this type.

Bioequivalence has been demonstrated between the applicant's OxyNorm Dispersa 20 mg orodispersible tablets (Napp Pharmaceuticals Ltd) and its respective reference product Oxynorm 20mg capsules (Napp Pharmaceuticals Ltd). As the 5 mg, 10 mg and 20 mg strengths of the product meets the biowaiver criteria specified in the current guideline on investigation of bioequivalence (CPMP/EWP/QWP/1401/98rev 1/Corr**), the results and conclusions of the bioequivalence study on the 20 mg strength can be extrapolated to the 5 mg and 10 mg strength tablet.

SAFETY

With the exception of the bioequivalence study, no new data were submitted and none are required for applications of this type. As the safety profile of oxycodone is well-known, no additional data were required. No new or unexpected safety concerns arose from the safety data from the bioequivalence study.

PRODUCT LITERATURE

The SmPCs, PIL and labelling are satisfactory.

BENEFIT-RISK ASSESSMENT

The quality of the products is acceptable, and no new non-clinical or clinical safety concerns have been identified. Bioequivalence has been demonstrated between the applicant's test product and its respective reference product. Extensive clinical experience with oxycodone is considered to have demonstrated the therapeutic value of the compound. The benefit-risk is, therefore, considered to be positive.

OXYNORM DISPERSA 5MG ORODISPERSIBLE TABLETS
OXYNORM DISPERSA 10MG ORODISPERSIBLE TABLETS
OXYNORM DISPERSA 20MG ORODISPERSIBLE TABLETS

PL 16950/0142
PL 16950/0143
PL 16950/0144

STEPS TAKEN FOR ASSESMENT

1 The MHRA received the marketing authorisation applications on 02 January 2007.

2 Following standard checks and communication with the applicant the MHRA considered the applications valid on 05 March 2007.

3 Following assessment of the application the MHRA requested further information on 13 November 2008, 23 November 2010 and 11 May 2011.

4 The applicant responded to the MHRA's requests, providing further information on 14 August 2009, 01 March 2011 and 14 July 2011.

5 The applications were determined on 18 December 2012.

OXYNORM DISPERSA 5MG ORODISPERSIBLE TABLETS
OXYNORM DISPERSA 10MG ORODISPERSIBLE TABLETS
OXYNORM DISPERSA 20MG ORODISPERSIBLE TABLETS

PL 16950/0142
PL 16950/0143
PL 16950/0144

STEPS TAKEN AFTER ASSESSMENT

Date submitted	Application type	Scope	Outcome

SUMMARY OF PRODUCT CHARACTERISTICS

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

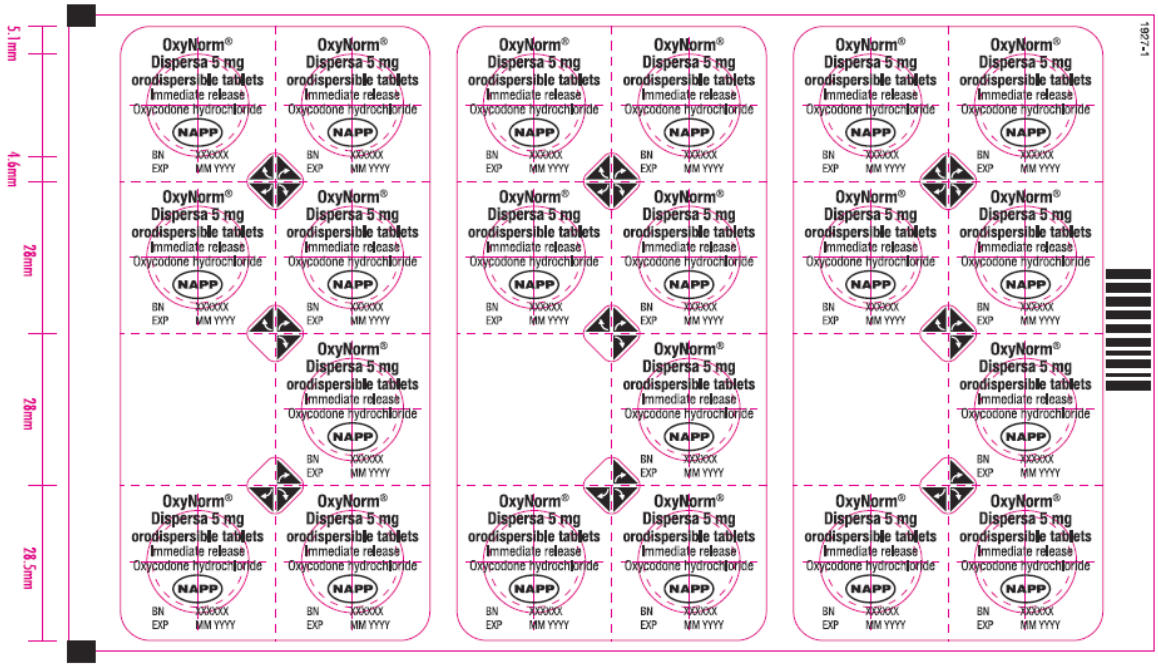
Module 3
PATIENT INFORMATION LEAFLET

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

LABELLING

CARTON:

BLISTER:


5.1mm
4.6mm
28mm
28mm
28.5mm
1927-1
OxyNorm®
Dispersa 5 mg
orodispersible tablets
Immediate release
Oxycodone hydrochloride
NAPP
BN xxxxx
EXP MM YYYY

CARTON:


OXYNORM DISPERSA 5 MG
OXYNORM DISPERSA 10 MG
OXYNORM DISPERSA 20 MG
9960-1
Napp Pharmaceuticals Ltd.,
Cambridge Science Park, Milton Road,
Cambridge CB4 0GW, UK.
Member of the Napp Pharmaceutical Group.
® OxyNorm and OXYNORM DISPERSA are registered trade marks of Mundipharma AG.
NAPP and the 'NAPP' device (logo) are registered trade marks of the Napp Pharmaceutical Group.
FLASHTAB and the 'FLASHTAB TECHNOLOGY' device (logo) are registered trade marks of Ethypharm S.A. and are used under licence.
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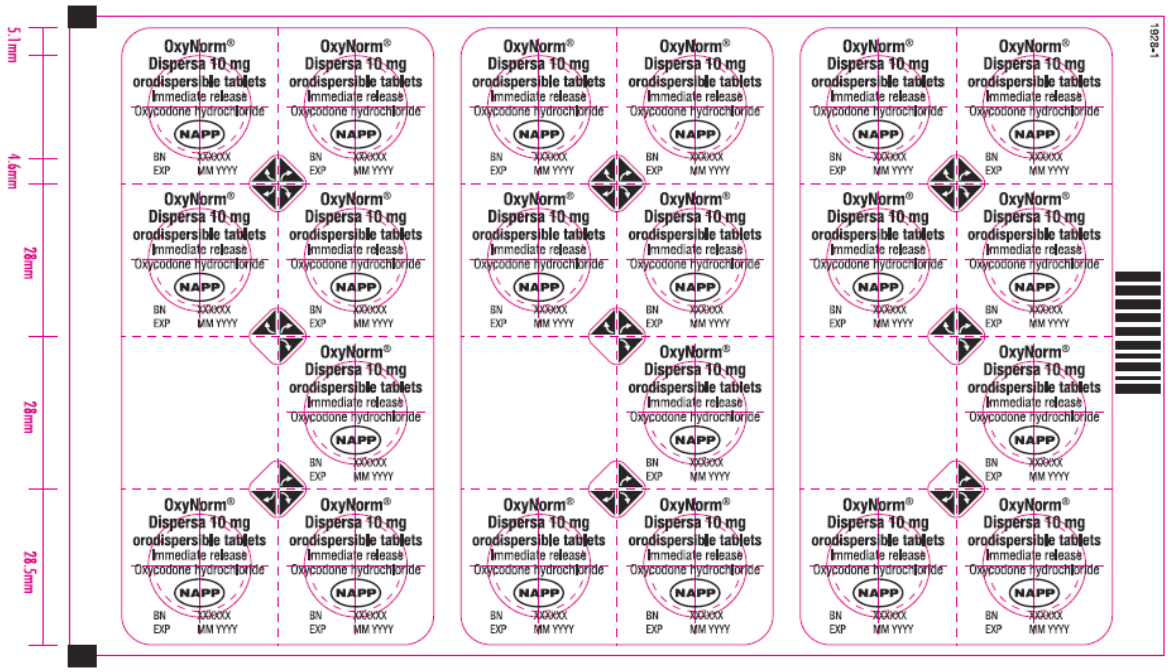
OxyNorm Dispersa®
orodispersible tablets
Oxycodone hydrochloride
10 mg
For oral use
28 tablets
NAPP
FLASHTAB TECHNOLOGY
28 tablets
10 mg
OxyNorm Dispersa®
orodispersible tablets
Oxycodone hydrochloride
BRC39
60x32x118mm
V1
5 012854 080584
OxyNorm Dispersa®
orodispersible tablets
Oxycodone hydrochloride
10 mg
28 tablets
Each orodispersible tablet contains 9 mg oxycodone as 10 mg oxycodone hydrochloride.
Also contains sucrose, maltodextrin and aspartame.
See leaflet for further information.
Dosage: To be taken as directed by your doctor.
Place tablet in the mouth where it disperses rapidly before swallowing.
Keep out of the reach and sight of children.
Read the package leaflet before use.
CD
POM
PL 16950/0143
APPLY PHARMACY LABEL IN THIS AREA
BN
MAN
EXP

BLISTER:


5.1mm
4.6mm
28mm
28mm
28.5mm
1928-1
OxyNorm®
Dispersa 10 mg
orodispersible tablets
Immediate release
Oxycodone hydrochloride
NAPP
BN XXXXX
EXP MM YYYY

CARTON:


9961-1
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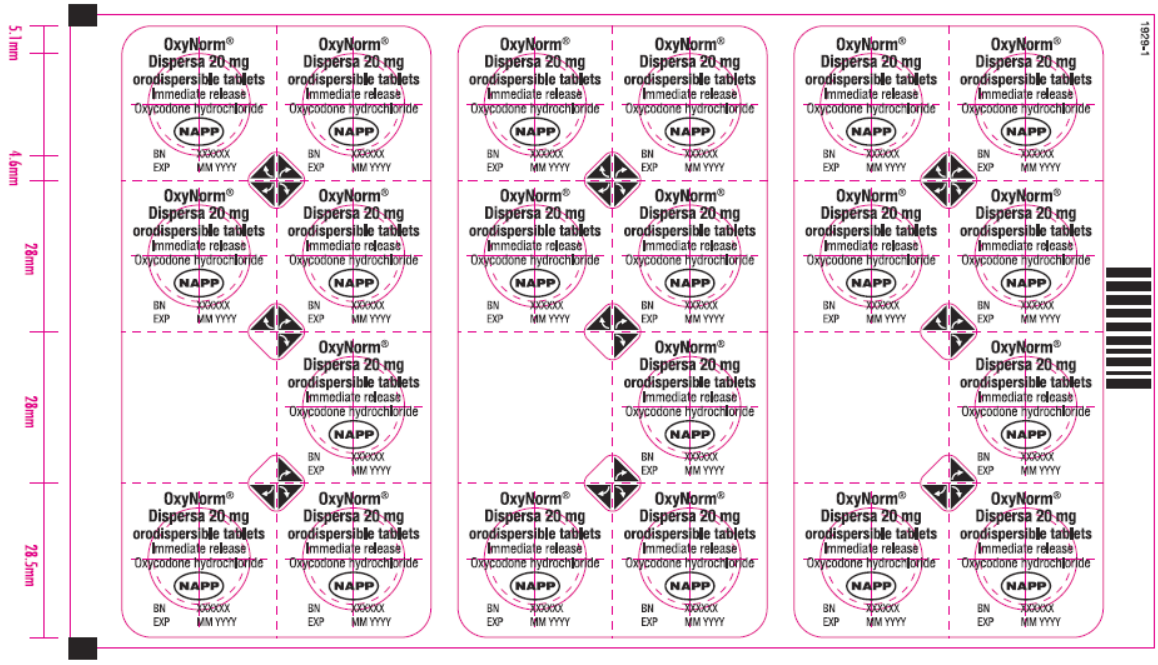
OxyNorm Dispersa®
orodispersible tablets
Oxycodone hydrochloride
20 mg
For oral use
28 tablets
NAPP
FLASHTAB TECHNOLOGY
28 tablets
20 mg
OxyNorm Dispersa®
orodispersible tablets
Oxycodone hydrochloride
BRC39
60x32x118mm
V1
5 012854 080591
OxyNorm Dispersa®
orodispersible tablets
Oxycodone hydrochloride
20 mg
28 tablets
Each orodispersible tablet contains 18 mg oxycodone as 20 mg oxycodone hydrochloride.
Also contains sucrose, maltodextrin and aspartame.
See leaflet for further information.
Dosage: To be taken as directed by your doctor.
Place tablet in the mouth where it disperses rapidly before swallowing.
Keep out of the reach and sight of children.
Read the package leaflet before use.
CD
POM
PL 16950/0144
APPLY PHARMACY LABEL IN THIS AREA
EN
MAN
EXP
OXYNORM DISPERSA 20 MG

BLISTER:


5.1mm
4.6mm
28mm
28mm
28.5mm
1929-1
OxyNorm®
Dispersa 20 mg
orodispersible tablets
Immediate release
Oxycodone hydrochloride
NAPP
BN XXXXX
EXP MM YYYY