Medicines & Healthcare products Regulatory Agency

MHRA Regulating Medicines and Medical Devices

Public Assessment Report

Decentralised Procedure

Nitrazepam 5 mg Tablets

(Nitrazepam)

Procedure No: UK/H/5975/001/DC

UK Licence No: PL 30139/0041

Intas Pharmaceuticals Limited

LAY SUMMARY

Nitrazepam 5 mg Tablets
(Nitrazepam)

This is a summary of the Public Assessment Report (PAR) for Nitrazepam 5 mg Tablets (PL 30139/0041; UK/H/5975/001/DC). It explains how the application for Nitrazepam 5 mg Tablets 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 Nitrazepam 5 mg Tablets.

For practical information about using Nitrazepam 5 mg Tablets, patients should read the package leaflet or contact their doctor or pharmacist.

Nitrazepam 5 mg Tablets may be referred to as 'Nitrazepam Tablets' in this Lay Summary.

What are Nitrazepam Tablets and what are they used for?

Nitrazepam Tablets are a 'generic medicine'. This means that Nitrazepam Tablets are similar to a 'reference medicine' already authorised in the UK called Mogadon 5 mg Tablets (PL 15142/0018; Meda Pharmaceuticals Ltd. UK).

Nitrazepam Tablets are used for the short term treatment of sleeplessness (also known as insomnia) when it is severe.

Nitrazepam Tablets help the patient to sleep but do not cure the underlying cause of the insomnia, which the patient should discuss with his/her doctor.

How do Nitrazepam Tablets work?

This medicine contains the active substance, nitrazepam. Nitrazepam shortens the time taken to fall asleep and lengthens the duration of sleep.

How are Nitrazepam Tablets used?

The pharmaceutical form of this medicine is a tablet and the route of administration is oral (by mouth). The tablets should be swallowed whole with water or another non-alcoholic drink.

The patient should always take this medicine exactly as his/her doctor has advised. The patient should not change the prescribed dose him/herself. The patient should check with his/her doctor or pharmacist if unsure about how to take this medicine.

The prescribing doctor will find the lowest dose to control the patient's symptoms.

The dose the doctor prescribes will depend on the nature of the patient's illness, his/her reaction to the medicine, the patient's age and bodyweight.

If the patient thinks that the effect of Nitrazepam Tablets is too weak or too strong, he/she should talk to their doctor.

Nitrazepam Tablet is not for use in children.

Please read section 3 of the package leaflet for detailed dosing recommendations, the route of administration, and the duration of treatment.

This medicine can only be obtained with a prescription.

What benefits of Nitrazepam Tablets been shown in studies?

As Nitrazepam Tablets are a generic medicine, studies in patients have been limited to tests to determine that they are bioequivalent to the reference medicine, Mogadan 5 mg Tablets (MEDA Pharma GmbH & Co. KG, Germany). As the German reference product used in the bioequivalence study is considered comparable to the corresponding reference product in the UK, bioequivalence has also been shown between the proposed product and the UK reference product Mogadon 5 mg Tablets; (Meda Pharmaceuticals Ltd. UK). Two medicines are bioequivalent when they produce the same levels of the active substance in the body.

What are the possible side effects of Nitrazepam Tablets?

Because Nitrazepam Tablets are a generic medicine and are bioequivalent to the reference medicine, their benefits and possible side effects are taken as being the same as those of the reference medicine.

For the full list of all side effects reported with Nitrazepam Tablets, see section 4 of the package leaflet or the Summary of Product Characteristics available on the MHRA website.

Also, for the full list of restrictions, see the package leaflet.

Why are Nitrazepam Tablets approved?

It was concluded that, in accordance with EU requirements, Nitrazepam Tablets have been shown to have comparable quality and to be bioequivalent to the reference medicine, Mogadan 5 mg Tablets (MEDA Pharma GmbH & Co. KG, Germany). Therefore, the view was that, as for Mogadan 5 mg Tablets (MEDA Pharma GmbH & Co. KG, Germany), the benefits of these tablets outweigh the identified risks.

What measures are being taken to ensure the safe and effective use of Nitrazepam Tablets?

A Risk Management Plan has been developed to ensure that Nitrazepam Tablets are used as safely as possible. Based on this plan, safety information has been included in the Summary of Product Characteristics and the package leaflet for Nitrazepam Tablets, including the appropriate precautions to be followed by healthcare professionals and patients.

Other information about Nitrazepam Tablets

Cyprus, Denmark, Estonia, Finland, Malta, Poland and the UK agreed to grant a Marketing Authorisation for Nitrazepam Tablets on 11 May 2016. A Marketing Authorisation was granted in the UK to Intas Pharmaceuticals Limited on 26 May 2016.

The full PAR for Nitrazepam Tablets follows this summary.

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

This summary was last updated in July 2016.

SCIENTIFIC DISCUSSION

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Scientific discussion

I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Member States considered that the application for Nitrazepam 5 mg Tablets (PL 30139/0041; UK/H/5975/001/DC) could be approved. This product is a prescription-only medicine (POM).

Nitrazepam 5 mg Tablets are indicated for the short-term treatment of insomnia when it is severe, disabling or subjecting the individual to unacceptable distress, where daytime sedation is acceptable. An underlying cause for insomnia should be sought before deciding upon the use of benzodiazepines for symptomatic relief. Benzodiazepines are not recommended for the primary treatment of psychotic illness.

Nitrazepam 5 mg Tablets may be referred to as 'Nitrazepam Tablets' in this report.

The application was submitted using the Decentralised Procedure (DCP), with the UK as Reference Member State (RMS), and Cyprus, Denmark, Estonia, Finland, Malta and Poland as Concerned Member States (CMS). The application was submitted under Article 10(1) of Directive 2001/83/EC, as amended, claiming to be a generic medicinal product of Mogadon 5 mg Tablets (PL 15142/0018 ; Meda Pharmaceuticals Limited, UK), which was authorised in the UK on 03 May 1999. Mogadon 5 mg Tablets (PL 15142/0018; Meda Pharmaceuticals Ltd. UK) refers to Mogadon 5mg Tablets (PL 00031/0062R; Roche) which was granted on 21 June 1983. The reference product has been authorised in the EU for more than 10 years, thus the period of data exclusivity has expired.

The active substance, nitrazepam, is a nitro-benzodiazepine derivative. Nitrazepam binds the GABAA receptor, increasing its activity via allosteric modification, more frequent channel opening, chloride ion conductance and inhibition of the action potential.

One single-dose, bioequivalence study was submitted to support this application, comparing the applicant's test product Nitrazepam 5mg tablets (Intas Pharmaceuticals Limited) and the reference product Mogadan 5 mg Tablets (Nitrazepam 5 mg tablets; MEDA Pharma GmbH & Co. KG, Germany) under fasting conditions. The applicant has stated that the bioequivalence study was conducted in compliance with Good Clinical Practice (GCP).

With the exception of the bioequivalence study, no new non-clinical or clinical data were submitted, which is acceptable given that the application was based on being a generic medicinal product of an originator product that has been in clinical use for over 10 years.

The RMS has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place at all sites responsible for the manufacture, assembly and batch release of this product. For manufacturing sites within the Community, the RMS has accepted satisfactory declarations that acceptable standards of GMP are in place at those sites.

For manufacturing sites outside the Community, the RMS has accepted copies of current GMP Certificates of satisfactory inspection summary reports, 'close-out letters' or 'exchange of information' issued by the inspection services of the competent authorities (or those countries with which the EEA has a Mutual Recognition Agreement for their own territories) as certification that acceptable standards of GMP are in place at those non-Community sites.

The RMS and CMS considered that the applications could be approved at the end of procedure (Day 210) on 11 May 2016. After a subsequent national phase, a licence was granted in the UK to Intas Pharmaceuticals Limited on 26 May 2016.

II. QUALITY ASPECTS

II.1 INTRODUCTION

The submitted documentation concerning the proposed product 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.

Nitrazepam Tablets are white to off white round, flat, bevel edged tablets, debossed with 'DM' on one side and plain on other side. Each tablet contains 5 mg of nitrazepam. The tablets also contain lactose monohydrate, maize starch, sodium starch glycolate (Type A), talc (E553b) and magnesium stearate. Appropriate justification for the inclusion of each excipient has been provided.

Nitrazepam Tablets are available in:

1. polyvinylchloride/ polyvinylidene chloride-aluminium blisters, in pack sizes of 10, 20, 25, 28, 30, 50, 60 and 100 tablets.
2. High density polyethylene containers, in pack sizes of 30, 500 and 1000 tablets.

Not all pack sizes may be marketed.

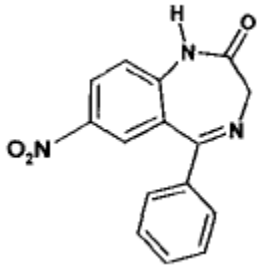
Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary packaging complies with the current European regulations concerning materials in contact with food.

II.2 DRUG SUBSTANCE

Nitrazepam

rINN: Nitrazepam
Chemical name(s): 7-Nitro-5-phenyl-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one;

Structure:



Molecular formula: $C_{15}H_{11}N_3O_3$
M_r 281.3
Appearance: A white or yellow crystalline powder
Solubility Practically insoluble in water, slightly soluble in ethanol (96 per cent)
Stereoisomerism Not applicable, as there are no chiral centres in the molecule.
Polymorphism Polymorphism in nitrazepam is not reported in the literature.

Nitrazepam is the subject of a European Pharmacopoeia monograph.

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

II.3 MEDICINAL PRODUCT

Pharmaceutical Development

The objective of the development programme was to formulate safe, efficacious, tablets containing 5 mg of nitrazepam per tablet that could be considered a generic version of the reference product Mogadan 5 mg tablets (MEDA Pharma GmbH & Co. KG., Germany). Suitable pharmaceutical development data have been provided for this application.

Comparative *in-vitro* dissolution and impurity profiles have been provided for this product and the reference product.

All the excipients comply with their respective European Pharmacopoeia monographs.

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 satisfactory batch formula has been provided for the manufacture of the product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated with full- scale batches and has shown satisfactory results.

Control of Finished Product

The finished product specification is acceptable. Test methods have been described and have been validated adequately. Batch data have been provided and comply with the release specifications. Certificates of Analysis have been provided for all 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 5 years has been accepted. This product does not require any special storage conditions.

Suitable post approval stability commitments have been provided to continue stability testing on batches of finished product.

Bioequivalence/Bioavailability

Satisfactory Certificates of Analysis have been provided for the test and reference batches used in the bioequivalence study. The bioequivalence study is discussed in Section IV, Clinical Aspects.

II.4 Discussion on chemical, pharmaceutical and biological aspects

It is recommended that a Marketing Authorisation is granted for Nitrazepam 5 mg Tablets.

III. NON-CLINICAL ASPECTS

III.1 Introduction

As the pharmacodynamic, pharmacokinetic and toxicological properties of nitrazepam are well-known, no new non-clinical data are required and none have been provided.

The applicant's 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

No new data have been submitted and none are required for an application of this type. Refer to Section III.1 Introduction, above.

III.3 Pharmacokinetics

No new data have been submitted and none are required for an application of this type. Refer to Section III.1 Introduction, above.

III.4 Toxicology

No new data have been submitted and none are required for an application of this type. Refer to Section III.1 Introduction, above.

III.5 Ecotoxicity/Environmental Risk Assessment (ERA)

Suitable justification has been provided for non-submission of an Environmental Risk Assessment. As the application is for a generic version of an already authorised product, it is not expected that environmental exposure will increase following approval of the Marketing Authorisation for the proposed product.

III.6 Discussion of the non-clinical aspects

No new non-clinical studies were conducted, which is acceptable given that the application was based on being a generic medicinal product of an originator product that has been licensed for over 10 years.

There are no objections to the approval of this application from a non-clinical viewpoint.

IV. CLINICAL ASPECTS

IV.1 Introduction.

The clinical pharmacology of nitrazepam is well-known.

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

In accordance with the regulatory requirements CPMP/EWP/QWP/1401/98 Rev 1/Corr**, Guideline on the Investigation of Bioequivalence, the Marketing Authorisation Holder submitted a bioequivalence study to support the application, comparing the applicant's test product Nitrazepam 5mg tablets (Intas Pharmaceuticals Limited) with the reference product Mogadan 5mg Tablets (MEDA Pharma GmbH & Co. KG, Germany) under fasting conditions.

With the exception of data generated from the bioequivalence study detailed below, no new pharmacodynamic or pharmacokinetic data are provided or required for this application.

IV.2 Pharmacokinetics

The clinical pharmacokinetic properties of nitrazepam are well-known. In support of the application, the Marketing Authorisation Holder submitted the following bioequivalence study:

An open label, balanced, randomised, two-treatment, two-period, two-sequence, single, oral dose, crossover, bioequivalence study to compare the pharmacokinetics of the applicant's test product Nitrazepam 5mg tablets (Intas Pharmaceuticals Limited) versus the reference product, Mogadan 5mg Tablets (MEDA Pharma GmbH & Co. KG, Germany) in healthy adult subjects under fasting conditions.

The subjects were administered a single oral dose (5 mg) of either the test or the reference product with about 240 ml of water, after at least a 10-hour overnight fast. Blood samples were collected before and up to and including 72 hours after each administration. The washout period between the treatment phases was 14 days. The pharmacokinetic results are presented below:

Table: Pharmacokinetic parameters (ratios and confidence intervals [CI]) of nitrazepam

Parameters	Geometric Least Squares Means			90% Confidence Interval	Power (%)
	Test Product-T	Reference Product-R	Ratio (T / R)(%)		
$\ln C_{max}$	53.203	58.886	90.3	83.36 - 97.93	99.8
$\ln AUC_{0-72}$	1335.077	1361.689	98.0	95.46 - 100.71	100.0

C_{max} maximum plasma concentration
AUC_{0-72} area under the plasma concentration-time curve from time zero to time 72 hour
Ratios and 90% CI calculated from ln-transformed data

Conclusion

The 90% confidence intervals of the test/reference ratio for AUC_{0-72} and C_{max} lie within the acceptable limits of 80.00% to 125.00%, in line with the 'Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1/Corr**). Thus, the data support the claim that the applicant's test product is bioequivalent to the reference product Mogadan 5mg Tablets (Nitrazepam tablets 5 mg; MEDA Pharma GmbH & Co. KG, Germany) under fasting conditions.

As the German reference product used in the bioequivalence study is considered comparable to the corresponding reference product in the UK, the claim of bioequivalence between the proposed product and the UK reference product (Mogadon 5 mg Tablets; Meda Pharmaceuticals Ltd. UK) can also be accepted.

IV.3 Pharmacodynamics

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

IV.4 Clinical Efficacy

The clinical efficacy of nitrazepam is well-known. No new efficacy data are presented for this type of application.

IV.5 Clinical Safety

With the exception of the safety data generated during the bioequivalence study no new safety data were submitted and none are required for this type of application. The safety profile of nitrazepam is

well-known. No new or unexpected safety issues were raised during the bioequivalence study.

IV.6 Risk Management Plan

The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Nitrazepam 5 mg Tablets.

The following table lists the summary of safety concerns which have been identified:

Important identified risk	• Anterograde amnesia • Impaired alertness • Physical and psychological dependence • Withdrawal phenomenon /Rebound phenomenon • Abnormal psychological reactions • Loss of efficacy to the hypnotic effects of short-acting benzodiazepines • Precipitation of suicide • Hypersensitivity • Use in patients with severe respiratory insufficiency or sleep apnoea syndrome • Use in patients with phobic or obsessional states or chronic psychosis • Use in patients with myasthenia gravis • Use in patients with hepatic and renal impairment • Use in combination with alcohol and other CNS depressants • Abuse and misuse
Important potential risk	• Nil
Missing information	• Use during pregnancy • Long term use

Appropriate pharmacovigilance and risk minimisation activities have been addressed.

IV.7 Discussion of the clinical aspects

It is recommended that a Marketing Authorisation is granted for Nitrazepam 5 mg Tablets.

V. USER CONSULTATION

A user consultation with target patient groups on the Patient Information Leaflet (PIL) has been performed on the basis of a bridging report making reference to the PILs for:

1. Mogadan 5 mg tablets (Meda; parent PIL 1), with respect to relevant clinical information.
2. Solifenacin succinate 5mg/10mg film-coated tablets (parent PIL 2), with respect to design and layout.

The bridging report has been found to be acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

QUALITY
The important quality characteristics of Nitrazepam 5 mg 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. As the pharmacokinetics, pharmacodynamics and toxicology of nitrazepam are well-known, no additional data were required.

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

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

Bioequivalence has been demonstrated between the applicant's product and the reference product Mogadan 5mg Tablets (MEDA Pharma GmbH & Co. KG, Germany) under fasting conditions.

As the German reference product used in the bioequivalence study is considered comparable to the corresponding reference product in the UK, the claim of bioequivalence between the proposed product and the UK reference product (Mogadon 5 mg Tablets; Meda Pharmaceuticals Ltd. UK) can be accepted.

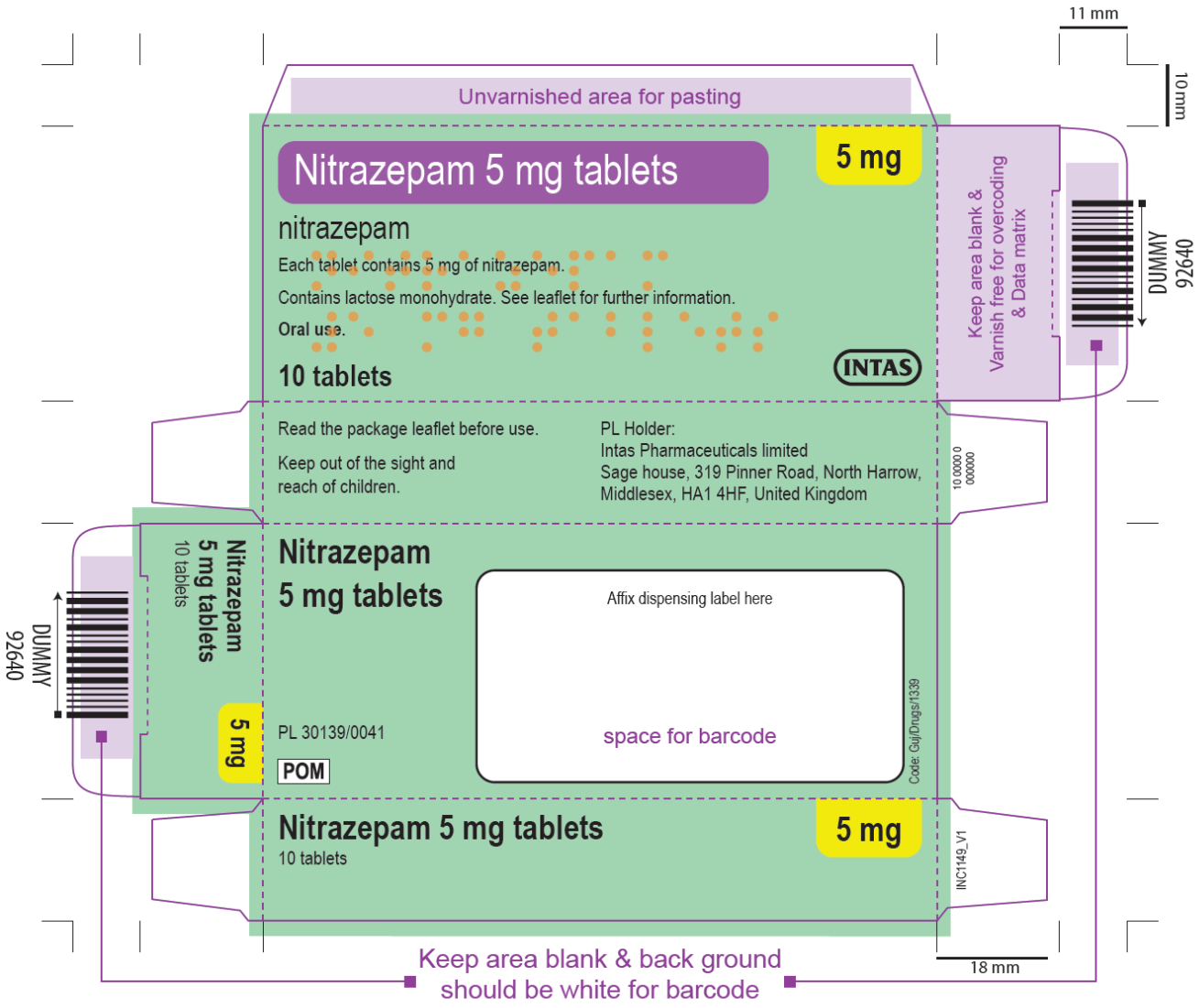
SAFETY
With the exception of the safety data from the bioequivalence study, no new data were submitted and none are required for an application of this type. As the safety profile of nitrazepam is well known, no additional data were required. No new or unexpected safety concerns arose from the bioequivalence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

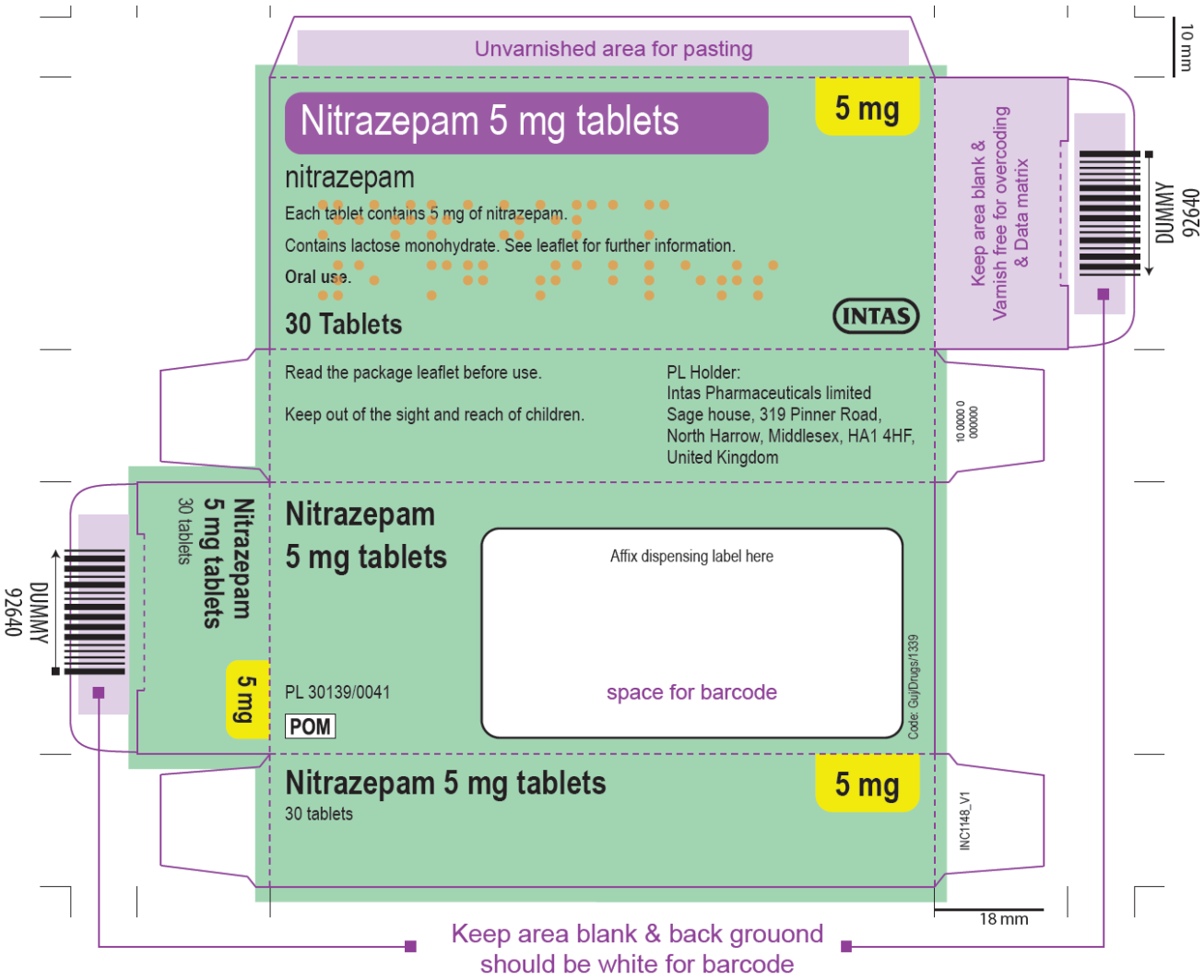
PRODUCT LITERATURE
The SmPC, PIL and labelling text are satisfactory and consistent with those for the reference product, where appropriate and in line with current guidance.

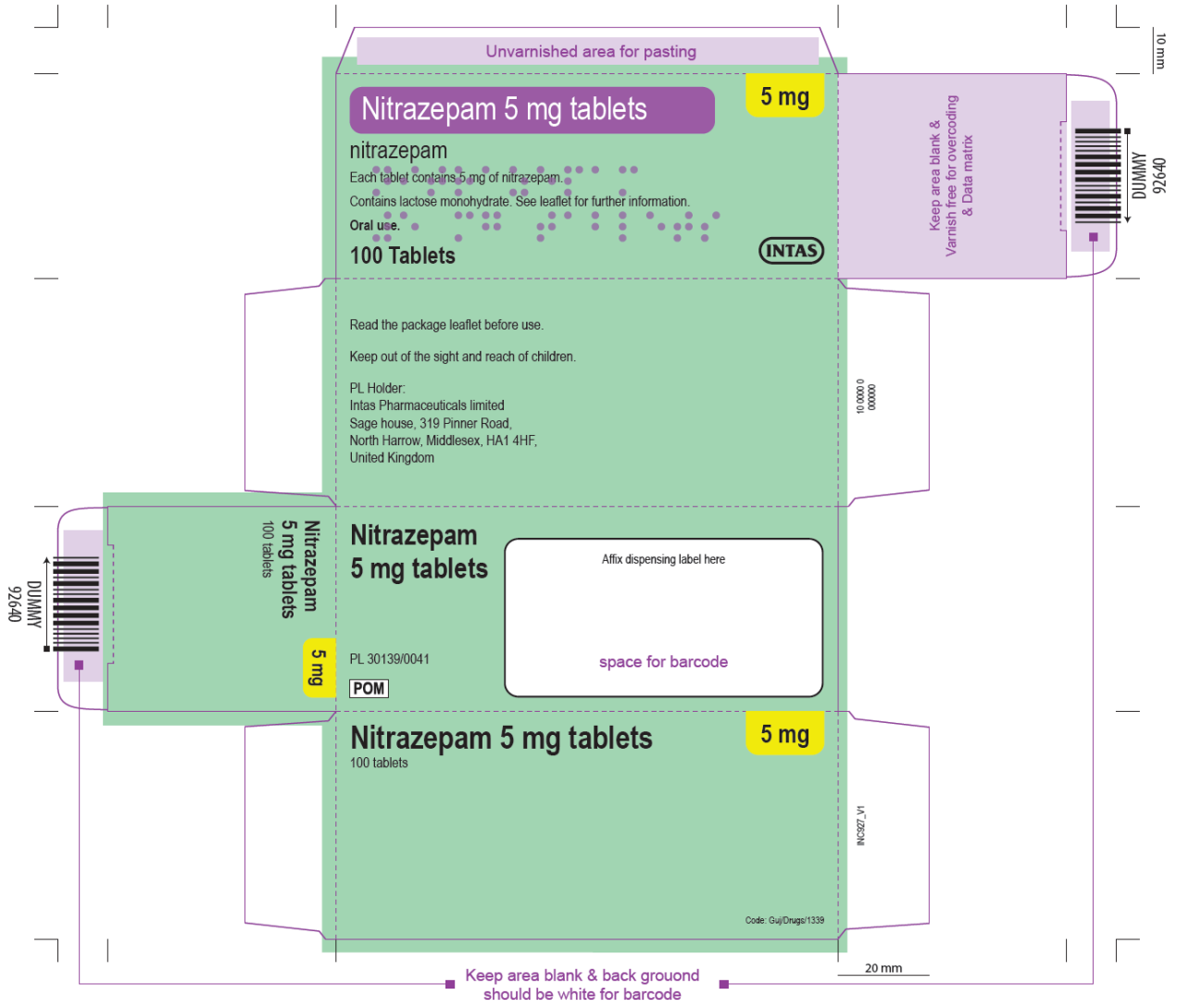
BENEFIT/RISK ASSESSMENT
The quality of the product is acceptable, and no new non-clinical or clinical safety concerns have been identified. Extensive clinical experience with nitrazepam is considered to have demonstrated the therapeutic value of the compound and bioequivalence to the reference product has been shown. The benefit/risk balance 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 SmPCs and package leaflets are available on the MHRA website. The current labelling is presented below:




Unvarnished area for pasting
10 mm
Nitrazepam 5 mg tablets
5 mg
nitrazepam
Each tablet contains 5 mg of nitrazepam.
Contains lactose monohydrate. See leaflet for further information.
Oral use.
30 Tablets
INTAS
Keep area blank & Varnish free for overcoding & Data matrix
DUMMY 92640
Read the package leaflet before use.
Keep out of the sight and reach of children.
PL Holder:
Intas Pharmaceuticals limited
Sage house, 319 Pinner Road,
North Harrow, Middlesex, HA1 4HF,
United Kingdom
10 0000 0 000000
Nitrazepam 5 mg tablets
30 tablets
5 mg
DUMMY 92640
Nitrazepam 5 mg tablets
Affix dispensing label here
space for barcode
PL 30139/0041
POM
Code: GujDrugs/1339
Nitrazepam 5 mg tablets
30 tablets
5 mg
INC1148_V1
18 mm
Keep area blank & back grouond should be white for barcode


Unvarnished area for pasting
Nitrazepam 5 mg tablets
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Keep area blank & Varnish free for overcoding & Data matrix
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Read the package leaflet before use.
Keep out of the sight and reach of children.
PL Holder:
Intas Pharmaceuticals limited
Sage house, 319 Pinner Road,
North Harrow, Middlesex, HA1 4HF,
United Kingdom
Nitrazepam 5 mg tablets
100 tablets
5 mg
DUMMY 92640
Nitrazepam 5 mg tablets
Affix dispensing label here
space for barcode
PL 30139/0041
POM
Nitrazepam 5 mg tablets
100 tablets
5 mg
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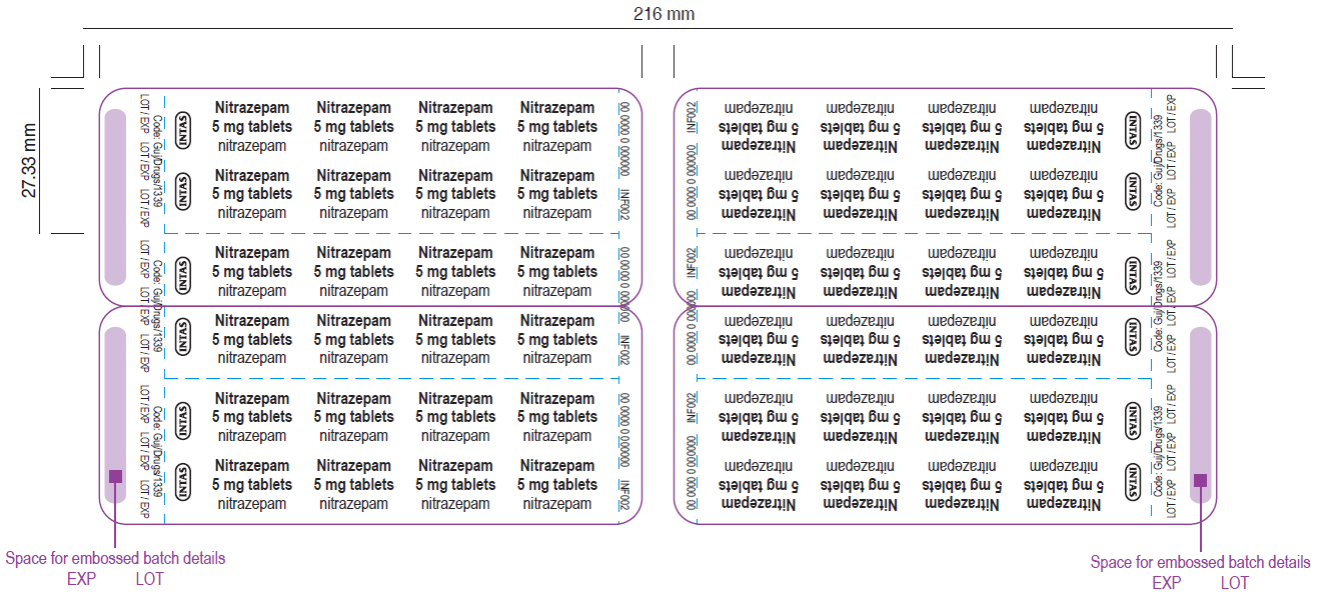
Keep area blank & back grouond should be white for barcode


216 mm
27.33 mm
Nitrazepam 5 mg tablets nitrazepam
INTAS
Code: Guj/Drugs/1339
LOT/EXP
Space for embossed batch details
EXP LOT
Space for embossed batch details
EXP LOT


DUMMY
Keep area blank &
Varnish free for
Lot and EXP
45 x 45 mm
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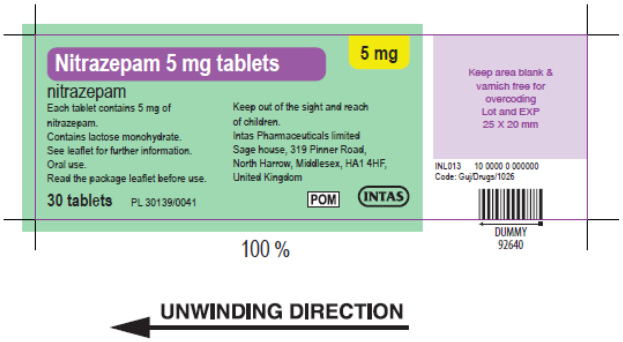
10 00000 0
INC5002_V1
Unvarnished area for pasting
5 mg
Nitrazepam
5 mg tablets
nitrazepam
Each tablet contains 5 mg
of nitrazepam.
Contains lactose monohydrate.
See leaflet for further information.
30 tablets
INTAS
5 mg
Nitrazepam
5 mg tablets
INTAS
DUMMY
92640
Nitrazepam
5 mg tablets
Oral use.
Read the package leaflet
before use.
Keep out of the sight and reach
of children.
POM
Code: Guj/Drugs/1339
5 mg
Nitrazepam
5 mg tablets
PL 30139/0041
Intas Pharmaceuticals limited
Sage house, 319 Pinner Road,
North Harrow, Middlesex,
HA1 4HF, United Kingdom
30 tablets
INTAS
Affix dispensing label here
space for barcode



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UNWINDING DIRECTION

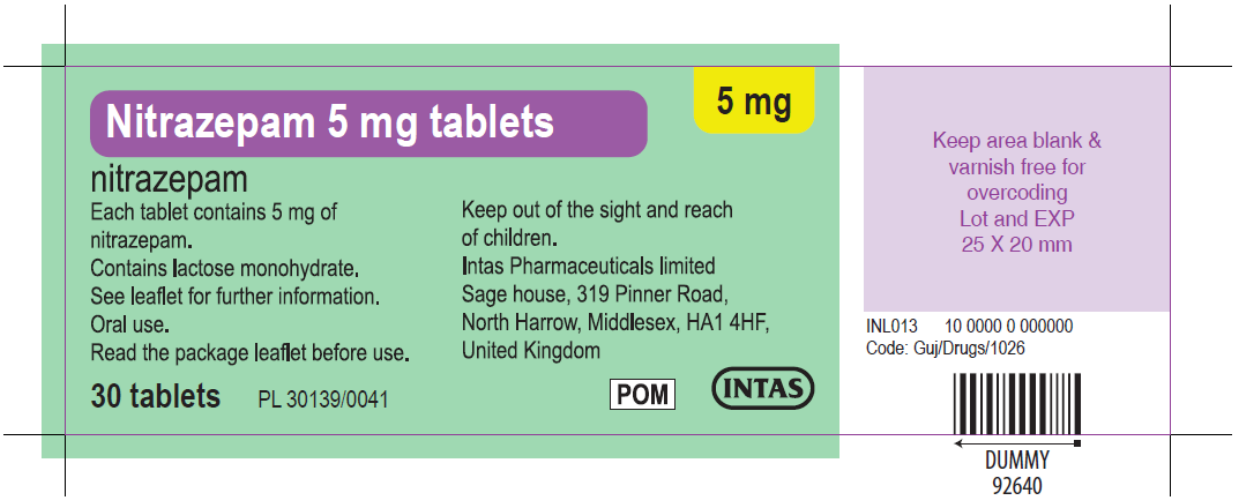

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Table of content of the PAR update for MRP and DCP

Steps taken after the initial procedure with an influence on the Public Assessment Report

Scope	Procedure number	Product information affected	Date of start of the procedure	Date of end of procedure	Approval/ non approval	Assessment report attached Y/N (version)