Medicines & Healthcare products Regulatory Agency

MHRA Regulating Medicines and Medical Devices

Public Assessment Report

UKPAR

Orobalin 1 mg film-coated tablets

(cyanocobalamin)

UK Licence Number: PL 48259/0045

Northumbria Pharma Ltd

LAY SUMMARY

Orobalin 1 mg film-coated tablets

(Cyanocobalamin)

This is a summary of the Public Assessment Report (PAR) for Orobalin 1 mg film-coated tablets (PL 48259/0045). It explains how the application for Orobalin 1 mg film-coated 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 Orobalin 1 mg film-coated tablets.

For ease of reading, the product may be referred to as 'Orobalin tablets' throughout the remainder of this lay summary.

For practical information about using Orobalin tablets, patients should read the package leaflet or contact their doctor or pharmacist.

What are Orobalin tablets and what are they used for?
Orobalin tablets are a 'generic medicine'. This means that Orobalin tablets are similar to a 'reference medicine' already authorised in the European Union called Betolvex 1 mg film-coated tablets (Actavis Group hf, Iceland).

Orobalin tablets are used to prevent and treat vitamin B12 deficiency.

Orobalin tablets are used to treat malabsorption of vitamin B12, this can be due to the absence of intrinsic factor, stomach surgery (stomach resection) or disease of the small intestine. It can also be used during para-aminosalicylic acid therapy, which can cause impaired B12 resorption.

How do Orobalin tablets work?
Orobalin tablets contain the active substance cyanocobalamin, which is known as vitamin B12.

Vitamin B12 is a vital vitamin and it is needed for normal cell division, normal production of blood and normal neurological function. Lack of vitamin B12 can result, for example, in the blood deficiency disease (pernicious anaemia) and/or symptoms of the neurological system, such as sensory disturbances.

Normally, vitamin B12 is provided in small amounts from food. It is absorbed by the body through the gastric acid and a special protein (intrinsic factor) which is formed in the gastric mucous. Vitamin B12 deficiency can develop if the vitamin cannot be absorbed normally from food by the body.

How are Orobalin tablets used?
The pharmaceutical form of Orobalin tablets is a film-coated tablet and this medicine is taken by mouth (orally).

Orobalin tablets can only be obtained with a prescription.

The patient should always take Orobalin tablets exactly as their doctor has advised. The patient should check with their doctor or pharmacist if they are not sure.

The dose should be decided by the patient's doctor, who will adjust it to a dose that best suits the patient.

Orobalin tablets should be taken between meals.

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

What benefits of Orobalin tablets have been shown in studies?
The Company provided data from studies to determine that Orobalin tablets are bioequivalent to the reference medicine, Betolvex 1 mg film-coated tablets (Actavis Group hf; Iceland). Two medicines are bioequivalent when they produce the same levels of the active substance in the body.

What are the possible side effects of Orobalin tablets?
As Orobalin tablets are a generic medicine and are bioequivalent to the reference medicine Betolvex 1 mg film-coated tablets (Actavis Group hf, Iceland), the benefits and possible side effects are taken as being the same as those for the reference product.

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

For the full list of all side effects reported with Orobalin tablets, see section 4 of the package leaflet available on the MHRA website.

If a patient gets any side effects, they should talk to their doctor, pharmacist or nurse. This includes any possible side effects not listed in the product information or the product information leaflet (PIL) that comes with the medicine. Patients can also report suspected side effects themselves, or a report can be made on behalf of someone else they care for, directly via the Yellow Card scheme at www.mhra.gov.uk/yellowcard or search for 'MHRA Yellow Card' online. By reporting side effects, patients can help provide more information on the safety of this medicine.

Why were Orobalin tablets approved?
It was concluded that, in accordance with UK and EU requirements, Orobalin tablets have been shown to have comparable quality and to be bioequivalent to Betolvex 1 mg film-coated tablets (Actavis Group hf, Iceland). Therefore, the MHRA decided that, as for Betolvex 1 mg film-coated tablets (Actavis Group hf, Iceland), the benefits are greater than the risks and recommended that they can be approved for use.

What measures are being taken to ensure the safe and effective use of Orobalin tablets?
A Risk Management Plan (RMP) has been developed to ensure that Orobalin tablets used as safely as possible. Based on this plan, safety information has been included in the Summary of Product Characteristics (SmPC) and the package leaflet for Orobalin 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 Orobalin tablets
A Marketing Authorisation was granted in the UK to Fontus Health Limited on 26 October 2018.

The Marketing Authorisation subsequently underwent a change of ownership procedure to the company, Northumbria Pharma Ltd (PL 48259/0045) on 04 January 2019.

The full PAR for Orobalin tablets follows this summary.

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

This summary was last updated in June 2021.

TABLE OF CONTENTS

I INTRODUCTION

Please note that the below scientific discussion consists of the <u>original</u> assessment of these product licences, plus a summary of key post approval changes to improve the accuracy of this Public Assessment Report.

The Medicines and Healthcare products Regulatory Agency (MHRA) granted Fontus Health Limited a Marketing Authorisation for the medicinal product Orobalin 1 mg film-coated tablets (PL 42924/0012) on 26 October 2018. For ease of reading, the product may be referred to 'Orobalin tablets' in this scientific discussion.

The product is a Prescription Only Medicine (legal classification POM) and is indicated for haematological, neurological and other symptoms secondary to vitamin B12 deficiency, including:

- Nutritional B12 deficiency
- Malabsorption of vitamin B12, such as due to the absence of intrinsic factor (pernicious anaemia), stomach resection or disease of the small intestine.

It is also indicated during para-aminosalicylic acid therapy, which can cause impaired B12 resorption.

This application was submitted under Article 10(1) of Directive 2001/83/EC, as amended (regulation 51 of The Human Medicines Regulation 2012, as amended), referring to the Danish reference product Betolvex 1 mg film-coated tablets (Actavis Group hf), which was granted in Denmark on 31 May 1983. Currently, there is no analogous 1 mg strength tablet on the UK market. The reference product is considered valid.

The active substance, cyanocobalamin, is a vitamin B12 analogue and is used for the treatment of pernicious anaemia, and nutritional deficiencies of vitamin B12 which results in macrocytic anaemia.

No new non-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.

No new clinical data have been submitted and none are required for this application. A suitable justification and supporting data for a Biopharmaceutics Classification System (BCS) Class III biowaiver have been provided.

The MHRA 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.

No new or unexpected safety concerns arose during review of information provided by the Marketing Authorisation Holder (MAH) and it was, therefore, judged that the benefits of Orobalin outweigh the risks and a Marketing Authorisation was granted.

The Marketing Authorisation subsequently underwent a change of ownership procedure to the company, Northumbria Pharma Ltd (PL 48259/0045) on 04 January 2019.

Summary of key post approval changes:

1. To update section 4.1 of the SmPC regarding a new addition to Orobalin is indicated for a variety of symptoms which are secondary to Vitamin B12 deficiency. (PL 48259/0045-0007 granted 18/05/2021).
   To note: the main body of this report (introduction section) has been updated with this indication change (PIL remains unchanged so no update to the lay summary is required). Please also refer to Annex 1 at the end of this PAR for further details.

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.

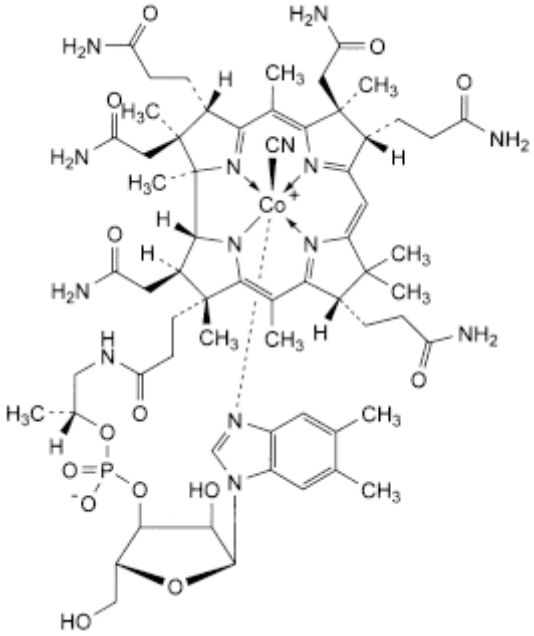
The product is a pink, round, convex film-coated tablet, plain on both sides and with an 8 mm diameter. Each tablet contains 1 mg of cyanocobalamin, as the active substance. The product also contains pharmaceutical excipients namely, microcrystalline cellulose, mannitol, pregelatinised starch, magnesium stearate, stearic acid, hypromellose, macrogol 400, titanium dioxide (E171), erythosine (E127) and yellow iron oxide (E172).

The finished product is packaged in aluminium-polyvinylchloride/polyvinylidene chloride blisters, in pack sizes of 20, 30, 60, 90 and 100 film-coated tablets.

Not all pack sizes may be marketed.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging components.

II.2 Drug Substance

INN:	Cyanocobalamin
Chemical name:	α-(5,6-dimethylbenzimidazol-1-yl) cobamide cyanide.
Structure:	
Molecular formula:	$C_{63}H_{88}CoN_{14}O_{14}P$
M_r:	1355
Description:	Dark red, crystalline powder or dark red crystals
Solubility	Cyanocobalamin is sparingly soluble in water and in ethanol (96 per cent), and practically insoluble in acetone.
Polymorphism	No polymorphism has been reported

Cyanocobalamin is the subject of a European Pharmacopoeia monograph.

All aspects of the manufacture and control of the active substance, cyanocobalamin, 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 1 mg of cyanocobalamin, that could be considered a generic medicinal product of the reference product Betolvex 1 mg film-coated tablets (Actavis Group hf, Iceland). A satisfactory account of the pharmaceutical development has been provided.

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

With the exception of yellow iron oxide (E172) and eryrthosine (E127), all excipients comply with their respective European Pharmacopoeia monographs. Yellow iron oxide (E172) and eryrthosine (E127) are controlled to suitable in-house specifications and are also in compliance with the current European Directives concerning the use of colouring agents in foodstuffs. Satisfactory Certificates of Analysis have been provided for all excipients. Suitable specifications and certificates of analysis data have been provided for each excipient.

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

This product does not contain or consist of genetically modified organisms (GMO).

Manufacture of the product

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 and has shown satisfactory results. Process validation data on production-scale batches have been provided.

Finished Product Specification

The release and shelf life finished product specifications proposed are acceptable. The test methods have been described that have been adequately validated. Batch data have been provided that comply with the release specification. 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 36 months, with the special storage conditions “Store below 25°C.” has been approved.

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

II.4 Discussion on chemical, pharmaceutical and biological aspects

There are no objections to the approval of this application, from a pharmaceutical viewpoint.

III NON-CLINICAL ASPECTS

III.1 Introduction

As the pharmacodynamic, pharmacokinetic and toxicological properties of cyanocobalamin are well-known, no new non-clinical studies are required, and none have been provided. An overview based on the literature review is, thus, appropriate.

The applicant’s non-clinical expert report 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 for this product type. Refer to section ‘III.1; Introduction’ detailed above.

III.3 Pharmacokinetics
Not applicable for this product type. Refer to section 'III.1; Introduction' detailed above.

III.4 Toxicology
Not applicable for this product type. Refer to section 'III.1; Introduction' detailed above.

III.5 Ecotoxicity/environmental risk assessment (ERA)
Since Orobalin tablets are intended for generic substitution, it is not anticipated to lead to an increased exposure of cyanocobalamin to the environment. An environmental risk assessment is therefore not deemed necessary.

III.6 Discussion on 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 a reference 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 cyanocobalamin is well-known. No new pharmacodynamic or pharmacokinetic data are provided or are required for this application.

The applicant has not submitted a bioequivalence study to support this application. A case for a BCS based biowaiver in accordance with Appendix III of the CHMP guideline on the investigation of bioequivalence (Doc. Ref.: CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **) has been submitted, as cyanocobalamin qualifies as BCS Class III compound. Appropriate comparative data have been provided against the reference product.

A comprehensive review of the published literature has been provided by the applicant, citing the well-established clinical pharmacology, efficacy and safety of cyanocobalamin.

The applicant's clinical overview has been written by an appropriately qualified person and is considered acceptable.

IV.2 Pharmacokinetics
The pharmacokinetic profile of cyanocobalamin is well known. No new clinical pharmacokinetic data are provided or required for this application.

The justification for a BCS Class III biowaiver can be accepted.

IV.3 Pharmacodynamics
The clinical efficacy of cyanocobalamin is well-known. No new pharmacodynamic data were submitted and none are required for this type of application.

IV.4 Clinical efficacy
The clinical efficacy of cyanocobalamin is well-known. No new efficacy data were submitted and none are required for this type of application.

IV.5 Clinical safety
No new safety data are presented for this application and none are required. The safety profile of cyanocobalamin is well-known and has been adequately summarised in the clinical overview. No new or unexpected safety concerns arose from this application.

IV.6 Risk Management Plan (RMP) and Pharmacovigilance System
The Marketing Authorisation Holder (MAH) has submitted a Risk Management Plan (RMP), in accordance with the requirements of Directive 2001/83/EC as amended (regulation 182 of The Human

Medicines Regulation 2012, as amended), describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Orobalin1 mg film-coated tablets.

A summary of safety concerns and planned risk minimisation activities, as approved in the RMP, is listed below:

Summary of safety concerns	
Important identified risks	Hypersensitivity reactions (anaphylactic reactions)
Important potential risks	None
Missing information	Use during pregnancy Use during breastfeeding

Routine pharmacovigilance and routine risk minimisation are proposed for all safety concerns.

IV.7 Discussion on the clinical aspects

The grant of a Marketing Authorisation is recommended for this application, from a clinical point of view.

V USER CONSULTATION

A package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC as amended (regulations 260(3) and 267(1) of The Human Medicines Regulation 2012, as amended). The language used for the purpose of user testing the pack leaflet was English.

The results show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

VI OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The quality of the product is acceptable, and no new non-clinical or clinical concerns have been identified.

A suitable justification and supporting data for a BCS Class III biowaiver has been accepted. Extensive clinical experience with cyanocobalamin is considered to have demonstrated the therapeutic value of the compound.

The benefit-risk is, therefore, considered to be positive.

The grant of a Marketing Authorisation is recommended

Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labels
The Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and labelling are satisfactory, in line with current guidelines and consistent with the reference product.

In accordance with legal requirements, the current approved UK versions of the SmPCs and PILs for this product are available on the MHRA website.

Representative copies of the labelling/label text are provided in Annex I.

TABLE OF CONTENT OF THE PAR UPDATE

Steps taken after the initial procedure with an influence on the Public Assessment Report (non-safety variations of clinical significance).

Please note that only non-safety variations of clinical significance are recorded below and in the annexes to this PAR. The assessment of safety variations where significant changes are made are recorded on the MHRA website or European Medicines Agency (EMA) website. Minor changes to the marketing authorisation are recorded in the current SmPC and/or PIL available on the MHRA website.

Application type	**Scope**	**Product information affected**	**Date of grant**	**Outcome**	**Assessment report attached Y/N**
Medical Type IB	PL 48259/0045-0007: To update section 4.1 of the SmPC regarding a new addition to Orobalin is indicated for a variety of symptoms which are secondary to Vitamin B12 deficiency.	SmPC and labelling	18/05/2021	Approved	Y-Annex 1

Annex I

Reference: **PL 48259/0045-0007**

Product: **Orobalin 1 mg film-coated tablets**

Type of Procedure: National

Submission category: Type IB Variation

Reason
To update section 4.1 of the SmPC regarding a new addition to Orobalin is indicated for a variety of symptoms which are secondary to vitamin B12 deficiency.

Supporting evidence
The Company has submitted an updated SmPC, labelling and clinical overview.

Evaluation
The applicant wishes to clarify the indication statement that Orobalin is indicated for the symptoms secondary to vitamin B12 deficiency, whether due to malabsorption or nutritional reasons.

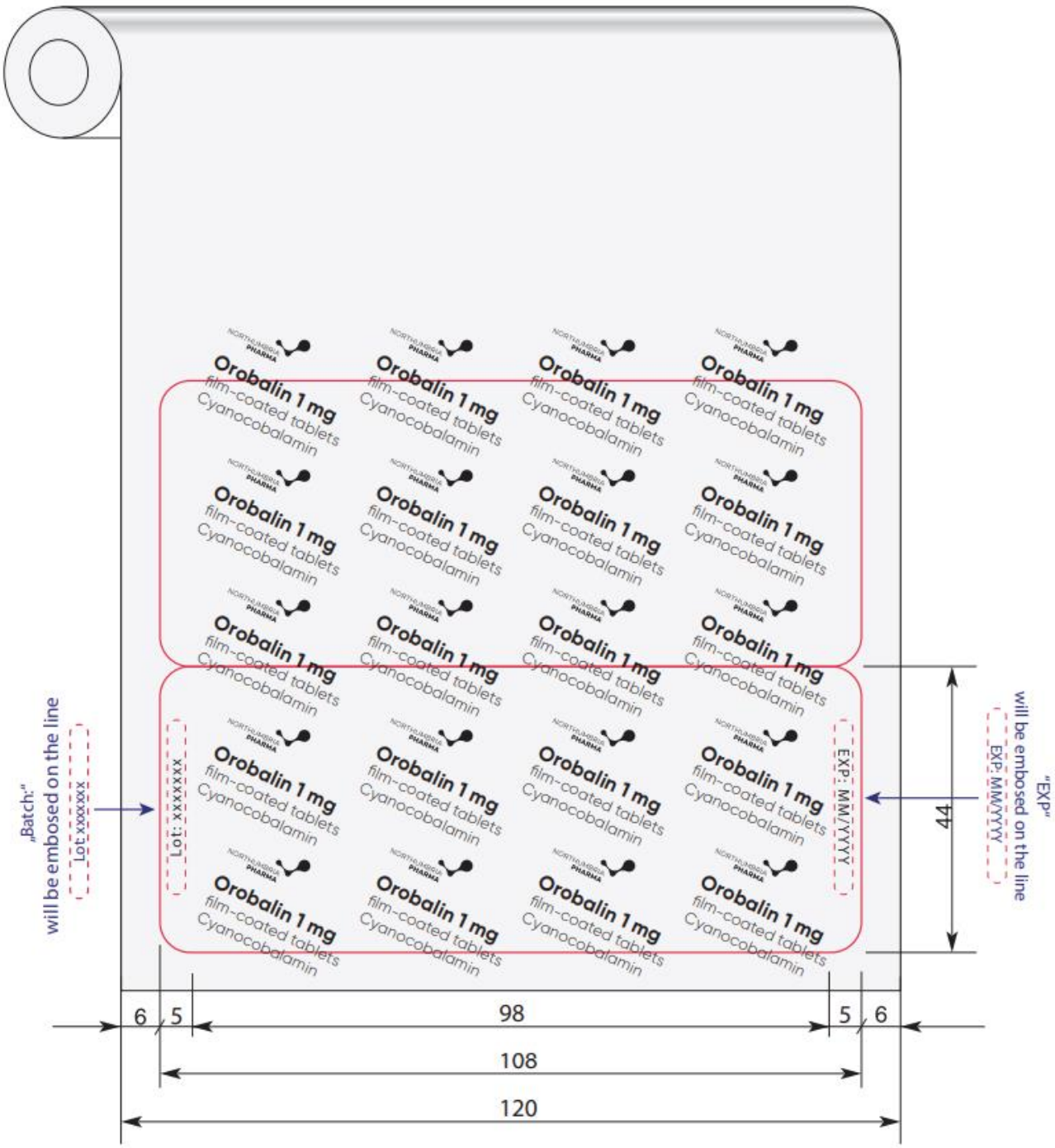
Adequate clinical information has been provided to support the requested variation.

Conclusion
The proposed changes are acceptable.

In accordance with legal requirements, the Summary of Product Characteristics (SmPCs) and Patient Information Leaflets (PILs) for products granted Marketing Authorisations at a national level are available on the MHRA website.

Representative current labelling is presented below:


Store below 25°C
Keep out of the sight and reach of children.
See leaflet for further information
Take as directed by your doctor.
Read the package leaflet before use.
Oral use.
Each film-coated tablet contains 1 mg Cyanocobalamin.
APFIX DISPENSING LABEL HERE
Orobalin
1 mg film-coated tablets
Cyanocobalamin
30 film-coated tablets
NORTHUMBRIA PHARMA
55979
Orobalin
1 mg film-coated tablets
Cyanocobalamin
30 film-coated tablets
Orobalin
1 mg film-coated tablets
Cyanocobalamin
30 film-coated tablets
1 mg
Orobalin
1 mg film-coated tablets
Cyanocobalamin
Marketing Authorisation Holder:
Northumbria Pharma Ltd
NETPark, Thomas Wright Way, Sedgefield,
County Durham, TS21 3FD UK
PL 48259/0045
POM
PC:
SN:
Lot:
EXP:
data printed on the production line during packing



Decision: Grant

Date: 18 May 2021.