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 42924/0012

Fontus Health Limited

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 42924/0012). 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?
Because 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.

Why were Orobalin tablets approved?
It was concluded that, in accordance with 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 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 December 2018.

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I INTRODUCTION

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. 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, 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.

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 (E 171), erythosine (E 127) and yellow iron oxide (E172).

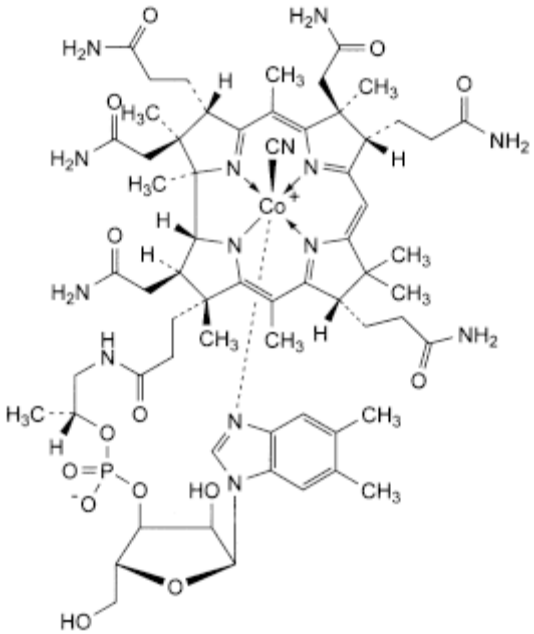
The finished product is packaged in aluminium-polyvinylchloride/polyvinylidene chloride blisters, in pack sizes of 20, 30, 60, 90 and 100 film-coated tablets.

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, 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. 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
In accordance with Directive 2010/84/EU, the current version of the Summary of Product Characteristics (SmPC) and Patient Information Leaflet (PIL) is available on the MHRA website.

The Marketing Authorisation Holder has submitted the text version only and has committed to submitting mock-ups to the regulatory authorities for approval before packs are marketed. The current labelling text is presented below:

PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING

Carton for Al-PVC/PVDC blisters and carton and label for HDPE bottles

1. NAME OF THE MEDICINAL PRODUCT

Orobalin 1 mg film-coated tablets
Cyanocobalamin

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 1 mg Cyanocobalamin.

3. LIST OF EXCIPIENTS

See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablets

Blisters
20 film-coated tablets
30 film-coated tablets
60 film-coated tablets
90 film-coated tablets
100 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Read the package leaflet before use. Take as directed by your doctor.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP:

9. SPECIAL STORAGE CONDITIONS

Store below 25°C

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Fontus Health Ltd
60 Lichfield Street,
Walsall. WS4 2BX.
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

PL 42924/0012

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

POM

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Orobalin 1 mg Film-Coated tablets

17. UNIQUE IDENTIFIER – 2D BARCODE

<2D barcode carrying the unique identifier included.>

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

< PC: {number} [product code]
SN: {number} [serial number]
NN: {number} [national reimbursement number or other national number identifying the medicinal product]>

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

Blister

1. NAME OF THE MEDICINAL PRODUCT

Orobalin 1 mg Film-Coated tablets
Cyanocobalamin

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Fontus Health Ltd

3. EXPIRY DATE

EXP:

4. BATCH NUMBER

Lot

5. OTHER

Orobalin 1 mg film-coated tablets

(cyanocobalamin)

PL 42924/0012

STEPS TAKEN AFTER AUTHORISATION - SUMMARY

Date submitted	Application type	Scope	Outcome