Public Assessment Report

Cyanocobalamin 50microgram film-coated tablets

(Cyanocobalamin)

UK Licence No: PL 30684/0243

DAWA Limited
LAY SUMMARY
Cyanocobalamin 50microgram film-coated tablets
(Cyanocobalamin)
This is a summary of the Public Assessment Report (PAR) for Cyanocobalamin 50microgram film-coated tablets (PL 30684/0243). It explains how Cyanocobalamin 50microgram film-coated tablets were assessed and their authorisation recommended, as well as the conditions of use. It is not intended to provide practical advice on how to use Cyanocobalamin 50microgram film-coated tablets.

This product will be referred to as Cyanocobalamin Tablets in this lay summary for ease of reading.

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

What are Cyanocobalamin Tablets and what are they used for?
Cyanocobalamin Tablets are a ‘generic medicine’. This means that Cyanocobalamin Tablets are similar to a ‘reference medicine’ already authorised in the UK called Cytacon 50micrograms Tablets/Cyanocobalamin 50micrograms Tablets (PL 10972/0028; Mercury Pharma Group Limited).

Cyanocobalamin Tablets are used to treat vitamin B12 deficiency when injections cannot be used.

How do Cyanocobalamin Tablets work?
Cyanocobalamin tablets contain the active ingredient cyanocobalamin, which is known as vitamin B12. This medicine helps to treat pernicious anaemia (reduction in the number of red blood cells) which is caused by lack of vitamin B12 in the body.

How are Cyanocobalamin Tablets used?
Cyanocobalamin Tablets are taken by mouth. The tablets must be swallowed with water and should be taken between meals. Patients should not stop taking this medicine unless advised by a doctor. The dosage may be adjusted at the discretion of a doctor.

The usual dosage in adults and elderly is one to three tablets daily.

The recommended dose in children is one tablet daily.

This medicine can be obtained from a pharmacy.

For further information on how Cyanocobalamin Tablets are used, please refer to the Summary of Product Characteristics and the Patient Information Leaflet available on the MHRA website.

How have Cyanocobalamin Tablets been studied?
Because Cyanocobalamin Tablets are a generic medicine, studies in patients have been limited to tests to determine that they are bioequivalent to the reference medicine, Cytacon 50micrograms Tablets/Cyanocobalamin 50micrograms Tablets. Two medicines are bioequivalent when they produce the same levels of the active substance in the body.

What are the benefits and risks of Cyanocobalamin Tablets?
Because Cyanocobalamin Tablets are a generic medicine, and are bioequivalent to the reference medicine, Cytacon 50micrograms Tablets/Cyanocobalamin 50micrograms Tablets, their benefits and risks are taken as being the same as the reference medicine.

Why are Cyanocobalamin Tablets approved?
It was concluded that, in accordance with EU requirements, Cyanocobalamin Tablets have been shown to have comparable quality and to be bioequivalent to Cytacon 50micrograms Tablets/Cyanocobalamin
50micrograms Tablets. Therefore, the view was that, as for Cytacon 50micrograms Tablets/Cyanocobalamin 50micrograms Tablets, the benefits outweigh the identified risks.

**What measures are being taken to ensure the safe and effective use of Cyanocobalamin Tablets?**
A risk management plan has been developed to ensure that Cyanocobalamin Tablets are used as safely as possible. Based on this plan, safety information has been included in the Summary of Product Characteristics (SmPC) and the PIL for Cyanocobalamin 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 and healthcare professionals will also be monitored and reviewed continuously.

**Other information about Cyanocobalamin Tablets**
A Marketing Authorisation was granted in the UK on 10 April 2017.

The full PAR for Cyanocobalamin Tablets follows this summary.

This summary was last updated in June 2017.
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I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Medicines and Healthcare products Regulatory Agency (MHRA) granted DAWA Limited, a Marketing Authorisation for the medicinal product Cyanocobalamin 50microgram film-coated tablets (PL 30684/0243) on 10 April 2017. The product can be obtained from a pharmacy and is used for the following indications:

- Treatment of nutritional Vitamin B12 deficiency.
- Treatment of vitamin B12 deficiency following partial gastrectomy.
- Treatment of tropical sprue, alone or with folic acid.
- Treatment of pernicious anaemia when parenteral administration is not possible or not advised.

This application was submitted according to Article 10(1) of Directive 2001/83/EC, as amended, claiming to be a generic medicinal product of the UK Reference Product, Cytacon 50micrograms Tablets/Cyanocobalamin 50micrograms Tablets, which was originally granted a Marketing Authorisation to Mercury Pharma Group Limited (PL 10972/0028) on 16 November 1993.

This medicine contains cyanocobalamin vitamin B12, which is used for the treatment of pernicious anaemia, and nutritional deficiencies of vitamin B12 which results in macrocytic anaemia.

No new non-clinical or clinical studies were provided with this application.

No bioequivalence study was submitted and this application is based on a Biopharmaceutics Classification System (BCS) class III biowaiver.

A satisfactory Risk Management Plan (RMP) and a summary of the pharmacovigilance system have been provided with this application.

No new or unexpected safety concerns arose during the review of information provided by the Marketing Authorisation Holder and it was, therefore, judged that the benefits of taking Cyanocobalamin 50microgram film-coated tablets outweigh the risks and a Marketing Authorisation was granted.
II QUALITY ASPECTS
II.1 Introduction
Each film-coated tablet contains 50 microgram cyanocobalamin, as an active ingredient. The excipients present in this product are cellulose microcrystalline, croscarmellose sodium, povidone, silica, colloidal anhydrous and magnesium stearate making up the tablet core, and the film coat composed of hypromellose, propylene glycol and titanium dioxide.

All excipients comply with their respective European Pharmacopoeia monographs. Satisfactory Certificates of Analysis have been provided for these excipients.

None of the excipients used contain material of animal or human. Confirmation has been given that the magnesium stearate used in the tablets is of vegetable origin.

The finished product is packaged either in a clear polyvinylchloride (PVC)/polyvinylidenechloride (PVdC)/aluminium blister packs containing 28, 56, 100 and 112 tablets, or in a securitainer (polypropylene container with a polyethylene cap) with a silica gel bag in packs containing 50 and 100 tablets.

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
INN: Cyanocobalamin
Chemical name(s): \(\alpha-(5,6\text{-Dimethylbenzimidazol-1-yl})\text{cobamide cyanide}\)

\[
\text{Molecular formula: } \text{C}_{63}\text{H}_{88}\text{CoN}_{14}\text{O}_{14}\text{P} \\
\text{Molecular weight: } 1355 \text{ g/mol} \\
\text{Appearance: } \text{A dark-red, crystalline powder or dark-red crystals. It is odourless and tasteless.} \\
\text{Solubility: } \text{Sparingly soluble in water and in alcohol, practically insoluble in acetone. The anhydrous substance is very hygroscopic.}
\]

Cyanocobalamin is the subject of a European Pharmacopoeia monograph.

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

II.3 Medicinal Product
Pharmaceutical Development
Suitable pharmaceutical development data have been provided for this application.

The physico-chemical properties of the drug product have been compared with those of the originator product. These data demonstrate that the proposed product can be considered a generic medicinal product of Cytacon 50micrograms Tablets/Cyanocobalamin 50micrograms Tablets.

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 commercial batches have been provided. The results are satisfactory.

Finished Product Specification
The finished product specification is satisfactory. The test methods have been described and have been adequately validated. Batch data have been provided that comply with the release specification. Certificates of Analysis have been provided for any working standards used.

Stability of the products
Finished product stability studies have been conducted in accordance with current guidelines and in the packaging proposed for marketing.

Based on the results, a shelf-life of 24 months for blister and securitainer with storage conditions of “Do not store above 25°C” and “Keep the blisters in the outer carton in order to protect from light” for blister and “Do not store above 25°C” and “Store in the original package in order to protect from light” for the securitainer are set. These are satisfactory.

II.4 Discussion on chemical, pharmaceutical and biological aspects
The grant of a Marketing Authorisation is recommended.

III NON-ClinICAL ASPECTS
III.1 Introduction
The pharmacodynamic, pharmacokinetic and toxicological properties of cyanocobalamin are well-known. The applicant has submitted a bibliographic review of the pharmacology, pharmacokinetics and toxicology of cyanocobalamin. 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. No new non-clinical data have been supplied with this application. This is acceptable.

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)
The Marketing Authorisation holder has provided adequate justification for not submitting an Environmental Risk Assessment (ERA). This is acceptable as vitamins are unlikely to result in significant risk to the environment.

III.6 Discussion on the non-clinical aspects
There are no objections to the approval of this product from a non-clinical point of view.
IV CLINICAL ASPECTS

IV.1 Introduction
For this generic application, the Applicant applied for a Biopharmaceutics Classification System (BCS) based biowaiver. No bioequivalence study was performed.

No new clinical data have been submitted and none are required for applications of this type. A clinical overview has been submitted to justify the biowaiver. The applicant’s clinical overview has been written by an appropriately qualified person and is considered acceptable.

IV.2 Pharmacokinetics
The Applicant applied for a Biopharmaceutics Classification System (BCS)-based biowaiver. In line with the ‘Note for Guidance on the investigation of bioavailability and bioequivalence’ (CPMP/EWP/QWP/1401/98 Rev 1/ Corr**), this was considered acceptable as cyanocobalamin is highly soluble (BCS class III) and the product is an immediate release solid dose preparation for oral use with the same pharmaceutical form as the reference product. Satisfactory data has been submitted to justify the BCS biowaiver.

IV.3 Pharmacodynamics
No new pharmacodynamics data were submitted and none were required for an application of this type.

IV.4 Clinical efficacy
No new efficacy data were submitted and none were required for an application of this type.

IV.5 Clinical safety
No new clinical safety data are required for this application and none have been submitted.

IV.6 Risk Management Plan (RMP)
The Marketing Authorisation Holder 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 Cyanocobalamin 50microgram film-coated tablets.
A summary of safety concerns and planned risk minimisation activities, as approved in the RMP, is listed below:

<table>
<thead>
<tr>
<th>Safety concern</th>
<th>Routine risk minimisation measures</th>
<th>Additional risk minimisation measures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Important identified risks</td>
<td>text in SmPC</td>
<td>None</td>
</tr>
<tr>
<td>Hypersensitivity Reactions</td>
<td>The product is contraindicated in case of “Hypersensitivity to the product or any of the excipients” in section 4.3 Contraindications of the SPC.</td>
<td>None</td>
</tr>
<tr>
<td>Important identified risks</td>
<td>Other routine risk minimisation measures</td>
<td>None</td>
</tr>
<tr>
<td>Need to monitor response to treatment for pernicious anaemia</td>
<td>text in SmPC 4.4 Special warnings and precautions for use For pernicious anaemia, an adequate dose must be used and the blood picture must be examined regularly at least every three months for 18 months until stabilised, and then annually. Indiscriminate administration of this medicine may mask precise diagnosis.</td>
<td>None</td>
</tr>
<tr>
<td>Should not be used to treat of megaloblastic anaemia due of pregnancy</td>
<td>text in SmPC 4.6 Pregnancy and lactation This medicine should not be used to treat megaloblastic anaemia of pregnancy because this is due to folate deficiency.</td>
<td>None</td>
</tr>
<tr>
<td>Important potential risks</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Missing information Preclinical safety</td>
<td>None</td>
<td>None</td>
</tr>
</tbody>
</table>

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.

V USER CONSULTATION
The 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. The language used for the purpose of user testing the PIL 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 labelling and package leaflet of medicinal products for human use.
VI OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

QUALITY
The quality of the product is acceptable and no new non-clinical or clinical concerns have been identified. 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.
Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and labelling
In accordance with Directive 2010/84/EU the Summaries of Product Characteristics (SmPCs) and Patient Information Leaflets (PILs) for products that are granted Marketing Authorisations at a national level are available on the MHRA website.

The approved labelling for Cyanocobalamin 50microgram film-coated tablets is presented below:
50 tablets
Cyanocobalamin 50 microgram Tablets
Vitamin B12

To be taken by mouth.
Use as directed by your doctor.

Dosage: Adults and Elderly - Usual dose is 1 to 3 tablets, daily between meals.
Children: Usual dose is 1 tablet, daily between meals.
Do not store above 25°C. Store in the original package in order to protect from light.
Keep out of the sight and reach of children.

Marburg Medium Pharmabrace Font
cyanocobalamin #50 mcg tablets

PL 30684/024
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Steps taken after the initial procedure with an influence on the Public Assessment Report

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<th>Application type</th>
<th>Scope</th>
<th>Outcome</th>
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