LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Betolvan
(cyanocobalamin)

SE/H/2607/001/MR

This module reflects the scientific discussion for the approval of Betolvan. The procedure was finalised on 2024-03-08. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, a marketing authorisation has been granted for Betolvan, 1 mg, film-coated tablet.

The active substance is cyanocobalamin. A comprehensive description of the indication and posology is given in the SmPC.

For recommendations to the marketing authorisation not falling under Article 21a/22a/22 of Directive 2001/83/EC and conditions to the marketing authorisation pursuant to Article 21a/22a/ 22 of Directive 2001/83/EC to the marketing authorisation, please see section VI.

The application for Betolvan, 1 mg, film-coated tablet, is a generic application submitted according to Article 10(1) of Directive 2001/83/EC. The applicant applies for a marketing authorisation in Sweden through a National Procedure.

The reference medicinal product chosen for the purposes of establishing the expiry of the data protection period is Betolvex, 1 mg, film-coated tablet, authorised in DK since 1983, with Teva B.V. as marketing authorisation holder.

European Reference Product (ERP)
A European Reference Product is used: Betolvex, 1 mg, film-coated tablet, authorised in DK since 1983, with Teva B.V. as marketing authorisation holder. The justification to use this product is based on information received from DK.

Potential similarity with orphan medicinal products
N/A

II. QUALITY ASPECTS

II.1 Drug Substance

The structure of the drug substance has been adequately proven and its physico-chemical properties are sufficiently described.

The manufacture of the drug substance has been adequately described and satisfactory specifications have been provided for starting materials, reagents and solvents.

The drug substance specification includes relevant tests and the limits for impurities and degradation products have been justified. The analytical methods applied are suitably described and validated.

Stability studies confirm the retest period.

II.2 Medicinal Product

The medicinal product is formulated using excipients listed in section 6.1 in the Summary of Product Characteristics.

The manufacturing process has been sufficiently described and critical steps identified.

The tests and limits in the specification are considered appropriate to control the quality of the finished product in relation to its intended purpose.

Stability studies have been performed and data presented support the shelf life and special precautions for storage claimed in the Summary of Product Characteristics, sections 6.3 and 6.4.

III. NON-CLINICAL ASPECTS

Pharmacology/Pharmacokinetics/Toxicology
Pharmacodynamic, pharmacokinetic and toxicological properties of cyanokobalamin are well known. As cyanokobalamin is a widely used, well-known active substance, no further studies are required and the applicant provides none. Overview based on literature review is, thus, appropriate.

Environmental Risk Assessment (ERA)
Since Betolvan is a generic product, it will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

There are no objections to approval of Betolvan from a non-clinical point of view.

IV. CLINICAL ASPECTS

Pharmacokinetics
Orally administrated cyanocobalamin is passively absorbed in the duodenum and small intestine even without the presence of intrinsic factor. The extent of absorption is dose dependent and approximately 1% of one dose of 1 mg (or 10-12 µg after one 1 mg tablet). The tablets should be taken between meals.

BCS-based biowaiver
The application is based on a Biopharmaceutical Classification System (BCS)-based biowaiver and no bioequivalence study has been submitted.

The applicant claims that cyanocobalamin is a BCS class III substance.

According to the ICH M9 Guideline on biopharmaceutics classification system-based biowaivers (EMA/CHMP/ICH/493213/2018), a BCS class III-based biowaiver is applicable for an immediate release product with systemic action if the drug substance is not considered to have a narrow therapeutic index and has been proven to exhibit high solubility and low permeability (BCS class III). Also, *in vitro* dissolution characteristics of the test and the reference product should be very rapid and all of the excipients should be qualitatively the same and quantitatively similar (except for film coating or capsule shell excipients). Excipients that may affect absorption should be qualitatively the same and quantitatively similar, i.e., within ± 10% of the amount of excipient in the reference product, and the cumulative difference for these excipients should be within ± 10%.

Discussion and overall conclusion
It is agreed that the submitted data indicate incomplete absorption and thus it is agreed to classify cyanocobalamin as a BCS class III substance from a pharmacokinetic perspective.

All the excipients in the applied for product are considered qualitatively the same and quantitatively similar (according to definition in ICH M9) to the excipients in the reference product, Betolvex.
Of the excipients used, mannitol is known to influence bioavailability and the quantity of mannitol in Betolvan is similar to that used in the reference product. This is agreed.

Cyanocobalamin is not considered to have a narrow therapeutic index.

The quality criteria for biowaiver (solubility and dissolution) have also been fulfilled.

It can be concluded that the drug substance has been proven to exhibit high solubility and limited absorption (BCS class III).

In conclusion, the justification for a BCS-based biowaiver can be accepted.

Pharmacodynamics/Clinical efficacy/Clinical safety
No new studies on pharmacodynamics, clinical efficacy or clinical safety have been submitted. Provided that bioequivalence with the originator product is demonstrated, additional data is not necessary.

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 Betolvan.

Part II Safety specification
The MAH has submitted the version 0.1 RMP dated 2022-10-13 and proposed the following summary safety concerns:

Summary of safety concerns	
Important identified risks	• None
Important potential risks	• None
Missing information	• None

Part III Pharmacovigilance Plan
Routine pharmacovigilance is suggested and no additional pharmacovigilance activities are proposed by the applicant, which is endorsed.

Part V Risk minimisation measures
Routine risk minimisation is suggested and no additional risk minimisation activities are proposed by the applicant, which is endorsed.

Part VI Summary of the RMP
The Summary of the RMP is endorsed.

Conclusion RMP assessment
The submitted Risk Management Plan, version 0.1 signed 2022-10-13 is considered acceptable.

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:
- At the request of the RMS;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time, but via different procedures.

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. The language used for the purpose of user testing the PL 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 generic product, Betolvan, is found adequate. There are no objections to approval of Betolvan from a non-clinical and clinical point of view. The absence of bioequivalence studies is acceptable. The product information is acceptable. The benefit/risk ratio is considered positive and the application is therefore recommended for approval.

List of recommendations not falling under Article 21a/22a/22 of Directive 2001/83/EC in case of a positive benefit risk assessment

N/A

List of conditions pursuant to Article 21a/22a or 22 of Directive 2001/83/EC

N/A

VII. APPROVAL

Betolvan, 1 mg, film-coated tablet was approved in the national procedure on 2024-03-08.

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Public Assessment Report – Update

Procedure number*	Scope	Product Information affected (Yes/No)	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse
SE/H/2607/001/MR	Initial Mutual Recognition Procedure	Yes	2024-11-14	Approval	N/A

*Only procedure qualifier, chronological number and grouping qualifier (when applicable)

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