LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Novavita
(cyanocobalamin)

SE/H/1577/01/DC

This module reflects the scientific discussion for the approval of Novavita. The procedure was finalised on 2017-01-27. For information on changes after this date please refer to the module 'Update'.

Postadress/Postal address: P.O. Box 26, SE-751 03 Uppsala, SWEDEN
Besöksadress/Visiting address: Dag Hammarskjölds väg 42, Uppsala
Telefon/Phone: +46 (0)18 17 46 00 Fax: +46 (0)18 54 85 66
Internet: www.mpa.se E-mail: registrator@mpa.se

I. INTRODUCTION

The application for Novavita, 1 mg, film-coated tablet, is a generic application made according to Article 10(1) of Directive 2001/83/EC. The applicant, Alternova A/S applies through the Decentralised Procedure with Sweden acting as reference member state (RMS) and FI as concerned member states (CMS).

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 Actavis Group hf as marketing authorisation holder.

For approved indications, see the Summary of Product Characteristics.

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

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

III.1 Discussion on the non-clinical aspects

Since this product has been shown to be essentially similar and refer to a product approved based on a full application with regard to preclinical data, no further such data have been submitted or are considered necessary.

IV. CLINICAL ASPECTS

IV.1 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.

No bioequivalence study has been submitted since the applicant applied for a BCS class III-based biowaiver.

The applicant states that crystalline cobalamins are known to be absorbed by passive diffusion to the extent of ±1% over a range of ±100 µg to 5 mg (Berlin et al., 1968; Carmel, 2008). Castelli et al (2011) showed an absolute bioavailability of 2.2% and 5.1% for a commercial and a new 5 mg cyanocobalamin tablet, respectively. In addition, studies have shown that 0.5 to 4% of radioactively labeled oral vitamin B12 can be absorbed by passive diffusion in both normal controls and patients with pernicious anemia (Doscherholmen et al., 1957; Berlin et al., 1968; Carmel, 2008). It is agreed that the data indicate incomplete absorption and thus it is agreed to classify cyanocobalamin as a BCS class III substance from a pharmacokinetic perspective.

Of the excipients used, mannitol is known to influence bioavailability and therefore approximately the same quantity of mannitol as in the reference product was used in Novavita. For a BCS class III biowaiver the guideline also states that all excipients should be qualitatively the same and quantitatively very similar. This is not entirely fulfilled for Novavita. However, considering the type of active substance the differences in excipients are considered acceptable for a BCS class III biowaiver and it is not considered likely that this difference would affect bioequivalence.

Cyanocobalamin is not considered to be a narrow therapeutic index drug.

From a quality perspective, *in vitro* dissolution tests have demonstrated very fast dissolution (>85% dissolved within 15 min) in all three media. Cyanocobalamin has high solubility.

The justification for BCS (Biopharmaceutics Classification System) based biowaiver CAN be accepted.

IV.2 Discussion on the clinical aspects

Since this product has been shown to be essentially similar and refer to a product approved based on a full application with regard to clinical efficacy/safety data, no further such data have been submitted or are considered necessary.

IV.3 Risk Management Plan

The MAH has submitted a risk management plan, RMP-215SEFI/1.0 signed 17th Sept 2015, 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 Novavita.

Safety specification

Summary table of safety concerns suggested in the RMP

Important identified risks	None
Important potential risks	-hypersensitivity reactions -Interactions with concomitant medicines
Missing information	None

Pharmacovigilance Plan

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

Risk minimisation measures

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

Summary of the RMP

The RMP is approvable.

V. USER CONSULTATION

A user consultation with target patient groups on the package information leaflet (PIL) has been performed on the basis of a bridging report making reference to Hydroxocobalamin E Consult 1 mg/ml solution for injection in procedure Dnr: 5.4.1-2013-64373. The bridging report submitted by the applicant has been found acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The quality of the generic product, Novavita, is found adequate. There are no objections to approval of Novavita, from a non-clinical and clinical point of view. The product information is acceptable.
The application is therefore recommended for approval.

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

N/A

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

N/A

VII. APPROVAL

The Decentralised procedure for Novavita, 1 mg, film-coated tablet was positively finalised on 2017-01-27.

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Public Assessment Report – Update

Procedure number*	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse

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

Postadress/Postal address: P.O. Box 26, SE-751 03 Uppsala, SWEDEN
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Internet: www.mpa.se E-mail: registrator@mpa.se