LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Hydroxocobalamin Pharmexon
(hydroxocobalamin acetate)

SE/H/2207/01/DC

This module reflects the scientific discussion for the approval of Hydroxocobalamin Pharmexon. The procedure was finalised on 2023-01-24. 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 Hydroxocobalamin Pharmexon, 1 mg/ml, Solution for injection.

The active substance is hydroxocobalamin acetate, hydroxocobalamin. 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 Hydroxocobalamin Pharmexon, 1 mg/ml, Solution for injection, is submitted according to Article 10a of Directive 2001/83/EC. The applicant, Pharmexon Consulting s.r.o. applies through the Decentralised Procedure with Sweden acting as reference member state (RMS) and Finland, Iceland and Norway as concerned member states (CMS).

Potential similarity with orphan medicinal products
According to the application form and a check of the Community Register of orphan medicinal products there is no medicinal product designated as an orphan medicinal product for a condition relating to the indication proposed in this application.

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 hydroxocobalamin are well known. As hydroxocobalamin 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. Upon on request, the applicant was asked to search relevant databases for existing published data on genotoxicity, carcinogenicity, and reprotoxicity to revise the overview with references in line with Article 10a of Directive 2001/83/EC. The applicant claim that they have searched relevant literature databases (e.g., PubMed) but has not succeeded to retrieve any new relevant literature. This indicates that there are no or very limited available publications on these topics.

Environmental Risk Assessment (ERA)

The applicant has provided a justification for the absence of a completed ERA based on that hydroxocobalamin is a vitamin and as such is not likely to result in a significant risk to the environment. The justification for absence of environmental risk assessment is considered acceptable.

IV. CLINICAL ASPECTS

Pharmacokinetics

No bioequivalence study or any other studies were performed by the Applicant on the proposed medicinal product. This is acceptable. According to the Applicant it can be assumed that the bioavailability of Hydroxocobalamin Pharmexon 1 mg/ml solution is similar to those hydroxocobalamin-products referred to in the literature, since the drug product is an aqueous solution containing the same concentration of the drug substance, the same comparable ingredients and is administered intramuscularly. This argumentation is found acceptable.

As this is an application according to Article 10a well established use, and hence a complete application, the bibliography should cover all aspects of pharmacokinetics in order to make a complete characterisation of the disposition of hydroxocobolamin following the intended route of administration.
Following IM administration, the Cmax of hydroxocobalamin is estimated at 22-72 nmol/L, Tmax at 60-480 minutes and AUC0-48 h between 8.7 and 76 μmol/L/min.
Vitamin B12 is extensively bound to specific plasma proteins called transcobalamins.
The great storage and long biological half-life (350-400 days in humans) of the vitamin provide substantial protection against periods of deprivation. Within 72 hours after IM injection of 0.5–1 mg of hydroxocobalamin, 16–66% of the dose may be excreted in urine. Renal excretion of parenterally administered vitamin increases with higher doses.
No PK data on special population or after subcutaneous administration were available.

Considering the extensive clinical use and experience of vitamin B12, the pharmacokinetics of hydroxocobalamin following intramuscular administration is on the overall found to be reasonably well described by the Applicant. The lack of PK data on sc administration is acceptable, as the use of sc hydroxocobalamin is considered well-established.

Pharmacodynamics

In humans, an exogenous source of vitamin B12 is required for nucleoprotein and myelin synthesis, cell reproduction, normal growth, and the maintenance of normal erythropoiesis.

Vitamin B12 is a part of two important enzyme reactions. In the first one deoxyadenosylcobalamin is a co-factor for the conversion of methylmalonyl-CoA to succinyl-CoA via the enzyme methylmalonyl-Coa mutas. In the event of B12 deficiency, this conversion cannot take place and the substrate methylmalonyl-CoA accumulates, resulting in the accumulation of the metabolite methylmalonic acid and to synthesizing of abnormal fatty acids which are accumulated in the cell membranes including in the CNS.

The second reaction requires methylcobalamin when 5-methyl-tetrahydrofolate is converted to tetrahydrofolate and homocysteine to methionine by the enzyme methionine synthetase (5-methyl-tetrahydrofolate homocysteine methyltransferase). In the event of B12 deficiency, 5-methyltetrahydrofolate (the “methyl folate trap”) and homocysteine accumulates. This leads to a deficiency of folate co-factors necessary for DNA syntheses.

Clinical efficacy

For a well-established use (WEU) application, the Applicant needs to demonstrate that the active substance of the medicinal product has been in well-established medicinal use for the claimed therapeutic indication within the Union for at least ten years, with recognized efficacy and an acceptable level of safety. The bibliographic application is based on published literature and seem to report a positive clinical response to injections with hydroxocobalamin or other related vitamin B12 substances.

Overall, included studies are considered to support the WEU-criteria regarding the degree of scientific interest in the use of the substance, reflected in the published scientific literature and the coherence of scientific assessments. The Applicant has proposed therapeutic use with hydroxocobalamin in pernicious anaemia other conditions with vitamin B12 deficiency and it is acknowledged that hydroxocobalamin is indeed a well-established therapy since more than 50 years for pernicious anaemia in particular, but also other disease states due to vitamin B12 deficiencies.

Overall, the articles presented by the applicant confirms the scientific interest for studies of the clinical efficacy of hydroxocobalamin and related vitamin B12 substances. Most of the studies seem to report a positive clinical response to vitamin B12.

Clinical safety

The Applicant has overall provided acceptable information regarding the clinical safety of hydroxocobalamin. Supportive to the safe use is that vitamin B12 has a documented long-standing use since the 1940´s. The WEU criteria regarding the time over which a substance has been used with regular application in patients; quantitative aspects of the use of the substance, taking into account the extent to which the substance has been used in practice, the extent of use on a geographical basis and the extent to which the use of the substance has been monitored by pharmacovigilance or other methods are considered supported.

The most commonly described adverse events regarding hydroxocobalamin are hypersensitivity reactions and skin and subcutaneous tissue disorders such as bullous eruptions. Furthermore, erythropoiesis is significantly increased after treatment start with hydroxocobalamin, causing hypokalaemia. Arrhythmias secondary to hypokalaemia have occurred at the beginning of parenteral treatment with hydroxocobalamin. However, no new alarming safety findings regarding

hydroxocobalamin have been presented by the Applicant. It is agreed that hydroxocobalamin is generally well tolerated.

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 Hydroxocobalamin Pharmexon.

Safety specification

Summary of safety concerns	
Important identified risks	-
Important potential risks	-
Missing information	-

The applicant proposes not to have any listed safety concerns in the updated RMP, version 2.0. Considering the well-known safety profile and long-standing use of vitamin B12, this is deemed acceptable.

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 MAH has satisfactorily responded to the questions raised and updated the RMP accordingly. The submitted Risk Management Plan, version 2.0 signed 24th of August 2022 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.

Periodic Safety Update Report (PSUR)

Active substance is currently listed in the published EURD list

With regard to PSUR submission, the MAH should take the following into account:

- PSURs shall be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal. Marketing authorisation holders shall continuously check the European medicines web-portal for the DLP and frequency of submission of the next PSUR.

- For medicinal products authorized under the legal basis of Article 10(1) or Article 10a of Directive 2001/83/EC, no routine PSURs need to be submitted, unless otherwise specified in the EURD list.

- In case the active substance will be removed in the future from the EURD list because the MAs have been withdrawn in all but one MS, the MAH shall contact that MS and propose DLP and frequency for further PSUR submissions together with a justification

V. USER CONSULTATION

A user consultation with target patient groups on the package information leaflet (PL) has been performed on the basis of a bridging report making reference to Hydroxocobalamin 1 mg/ml solution for injection, UK/H/6628/001/DC.
The bridging report submitted by the applicant has been found acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Overall, included studies are considered to support the WEU criteria regarding the degree of scientific interest in the use of the substance (reflected in the published scientific literature) and the coherence of scientific assessments. Also, the WEU criteria regarding the time over which a substance has been used with regular application in patients and quantitative aspects of the use of the substance are considered supported.

The Applicant has proposed therapeutic use with hydroxocobalamin in pernicious anaemia and other conditions with vitamin B12 deficiency where oral supplementation is not considered sufficient or else appropriate, which is acceptable. It is acknowledged that hydroxocobalamin is indeed a well-established therapy since more than 50 years for pernicious anaemia in particular, but also other disease states due to vitamin B12 deficiencies. Overall, the articles presented by the applicant confirms the scientific interest for studies of the clinical efficacy of hydroxocobalamin. Most of the studies seem to report a positive clinical response to hydroxocobalamin and other related vitamin B12 substances.

The most commonly described adverse events regarding hydroxocobalamin are hypersensitivity reactions and skin and subcutaneous tissue disorders such as bullous eruptions. Furthermore, erythropoiesis is significantly increased after treatment start with hydroxocobalamin, causing hypokalaemia. Arrhythmias secondary to hypokalaemia have occurred at the beginning of parenteral treatment with hydroxocobalamin. However, no new alarming safety findings regarding hydroxocobalamin have been presented by the Applicant. It is agreed that hydroxocobalamin is generally well tolerated.

The benefit/risk ratio is considered positive and Hydroxocobalamin Pharmexon, 1 mg/ml, Solution for injection is 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

The decentralised procedure for Hydroxocobalamin Pharmexon, 1 mg/ml, Solution for injection was positively finalised on 2023-01-24.

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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

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

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