Medicines & Healthcare products Regulatory Agency

MHRA Regulating Medicines and Medical Devices

Public Assessment Report

Decentralised Procedure

Hydroxocobalamin 1mg/ml Solution for Injection

(Hydroxocobalamin acetate)

Procedure No: UK/H/6628/001/DC

UK Licence No: PL 21597/0060

G L Pharma GmbH

LAY SUMMARY

Hydroxocobalamin 1mg/ml Solution for Injection

(Hydroxocobalamin acetate)

This is a summary of the Public Assessment Report (PAR) for Hydroxocobalamin 1mg/ml Solution for Injection (PL 21597/0060 formerly PL 08215/0108; UK/H/6628/001/DC). For ease of reading, the product may be referred to as Hydroxocobalamin injection in this lay summary. The lay summary explains how the application for Hydroxocobalamin injection was assessed and the authorisation recommended, as well as the conditions of use. It is not intended to provide practical advice on how to use Hydroxocobalamin injection. For practical information about using Hydroxocobalamin injection, patients should read the package leaflet or contact their doctor or pharmacist.

What is Hydroxocobalamin injection and what is it used for?

Hydroxocobalamin injection is a 'generic medicine'. This means that Hydroxocobalamin injection is similar to a 'reference medicine' containing the same active substance already authorised in the UK called Neo-Cytamen 1000 micrograms/ml solution for injection (RPH Pharmaceuticals AB).

Hydroxocobalamin injection is an injection which contains hydroxocobalamin acetate. It is used to treat deficiency of vitamin B12 which causes various types of anaemia (reduction in the number of red blood cells). Most people get enough vitamin B12 from their food, but if a person has had stomach surgery, or certain diseases of the intestines, or a restricted diet, he/she may not absorb enough vitamin B12. Hydroxocobalamin injection is also used to treat conditions called tobacco amblyopia and Leber's optic atrophy, which result in dimming of vision.

How does Hydroxocobalamin injection work?

Hydroxocobalamin injection is an injection which contains hydroxocobalamin acetate, which is known as vitamin B12. Hydroxocobalamin acetate is an essential nutrient for the functioning of the body.

How is Hydroxocobalamin injection used?

The product is available in the pharmaceutical form solution for injection.

Hydroxocobalamin injection is administered by injection into a muscle by a healthcare professional.

The patient's doctor will decide the correct dose for the patient depending on the patient's circumstances. The patient will be given a starting dose and then a maintenance dose.

The injection may need to be repeated depending on the patient's response. Hydroxocobalamin injection is suitable for use in adults as well as children and the elderly.

Please read section 3 of the package leaflet for detailed information on dosing recommendations, the route of administration and the duration of treatment.

Hydroxocobalamin injection can only be obtained on prescription.

What benefits of Hydroxocobalamin injection have been shown in studies?

As Hydroxocobalamin injection is a generic medicine, studies in patients have been limited to tests to determine that this medicine is bioequivalent to the reference medicine, Neo-Cytamen 1000 micrograms/ml solution for injection (RPH Pharmaceuticals AB). Two medicines are bioequivalent

when they produce the same levels of the active substance in the body.

What are the possible side effects of Hydroxocobalamin injection?
Like all medicines, Hydroxocobalamin injection can cause side effects, although not everybody gets them.

Since Hydroxocobalamin injection is a generic medicine of the reference medicine Neo-Cytamen 1000 micrograms/ml solution for injection (RPH Pharmaceuticals AB), the benefits and possible side effects are taken as being the same as for the reference medicine.

For the full list of all side effects reported with Hydroxocobalamin injection, see section 4 of the package leaflet.

For the full list of restrictions, see the package leaflet for Hydroxocobalamin injection.

Why is Hydroxocobalamin injection approved?
It was concluded that, in accordance with EU requirements, Hydroxocobalamin injection has been shown to have comparable quality and to be bioequivalent to Neo-Cytamen 1000 micrograms/ml solution for injection (RPH Pharmaceuticals AB). Therefore, the view was that, as for Neo-Cytamen 1000 micrograms/ml solution for injection (RPH Pharmaceuticals AB), the benefits outweigh the identified risks.

What measures are being taken to ensure the safe and effective use of Hydroxocobalamin injection?
A Risk Management Plan has been developed to ensure that Hydroxocobalamin injection is 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 Hydroxocobalamin injection, including the appropriate precautions to be followed by healthcare professionals and patients.

Other information about Hydroxocobalamin injection
Agreement for granting a Marketing Authorisation was given on 21 May 2018 by the UK and Ireland. A Marketing Authorisation for Hydroxocobalamin was granted in the UK to Kent Pharmaceuticals Limited on 18 June 2018. Subsequent to a change of ownership procedure, the Marketing Authorisation was transferred to G.L. Pharma GmbH (PL 21597/0060) on 13 July 2018.

The full PAR approved for Hydroxocobalamin injection follows this summary.

For more information about treatment with Hydroxocobalamin injection, read the package leaflet, or contact your doctor or pharmacist.

This summary was last updated in August 2018.

SCIENTIFIC DISCUSSION

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Scientific discussion

I. INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the UK and Ireland considered that the application for Hydroxocobalamin 1mg/ml Solution for Injection (PL 21597/0060, formerly PL 08215/0108; UK/H/6628/001/DC) could be approved. For ease of reading, the product may be referred to as Hydroxocobalamin injection in this scientific discussion. The product is a Prescription Only Medicine (POM) and is indicated in the treatment of Addisonian pernicious anaemia, prophylaxis and treatment of other macrocytic anaemias associated with vitamin B12 deficiency, tobacco amblyopia and Leber's optic atrophy.

This product contains the active substance hydroxocobalamin (as hydroxocobalamin acetate). Hydroxocobalamin is a cobalt-containing corrinoid. It is one of a group of cobalt-containing compounds, commonly known as vitamin B_{12}, of which hydroxocobalamin and cyanocobalamin, are the principal forms.

Vitamin B_{12} functions primarily as a coenzyme in nucleic acid synthesis, amino acid metabolism and fatty acid metabolism, with particular influence on the nervous system, bone marrow and haematopoiesis.

The application was submitted using the Decentralised Procedure, with the UK as Reference Member State (RMS) and Ireland as Concerned Member State (CMS). The application was submitted under Article 10(1) of Directive 2001/83/EC, as amended, as a generic application. The application refers to Neo-Cytamen 1000 microgams/ml solution for injection (RPH Pharmaceuticals; PL 36301/0011), which was authorised in the UK on 19 August 2010 following a change of ownership procedure of Neo-Cytamen Injection 1000mcg/Hydroxocobalamin Injection 1000mcg (PL 00039/0405). Neo-Cytamen Injection 1000mcg/Hydroxocobalamin Injection 1000mcg (PL 00039/0405; UCB Pharma Limited) was approved on 14 October 1992.

No new non-clinical studies were performed, which is acceptable given that the application was based on being a generic application 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 an application of this type.

According to CHMP guidelines, bioequivalence studies are not generally required for aqueous parenteral solutions (CPMP/EWP/QWP/1401/98. Rev. 1/Corr**, guideline on the investigation of bioequivalence).

The RMS 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.

For manufacturing sites within the Community, the RMS has accepted copies of current manufacturing authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

The UK and Ireland considered that the application could be approved at the end of procedure (Day 210) on 21 May 2018. After a subsequent national phase, a Marketing Authorisation was granted in the UK to Kent Pharmaceuticals Limited on 18 June 2018. Subsequent to a change of ownership procedure, the Marketing Authorisation was transferred to G.L. Pharma GmbH (PL 21597/0060) on 13 July 2018.

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 red, clear solution for injection.

Each 1ml of solution for injection contains 1.045 mg hydroxocobalamin acetate equivalent to 1 mg hydroxocobalamin (vitamin B_{12}). 1mg/ml of hydroxocobalamin equals 1000 micrograms/ml.

The product also contains pharmaceutical excipients, namely sodium hydroxide, glacial acetic acid, sodium chloride and water for injections.

Hydroxocobalamin is packaged in clear 1 ml glass ampoules, in a pack size of 5 x 1 ml ampoules.

Satisfactory specifications and Certificates of Analysis for the primary packaging material have been provided. The primary packaging is controlled to European Pharmacopoeia standards that comply with guidance concerning materials in contact with parenteral products.

II.2 DRUG SUBSTANCE

Hydroxocobalamin acetate

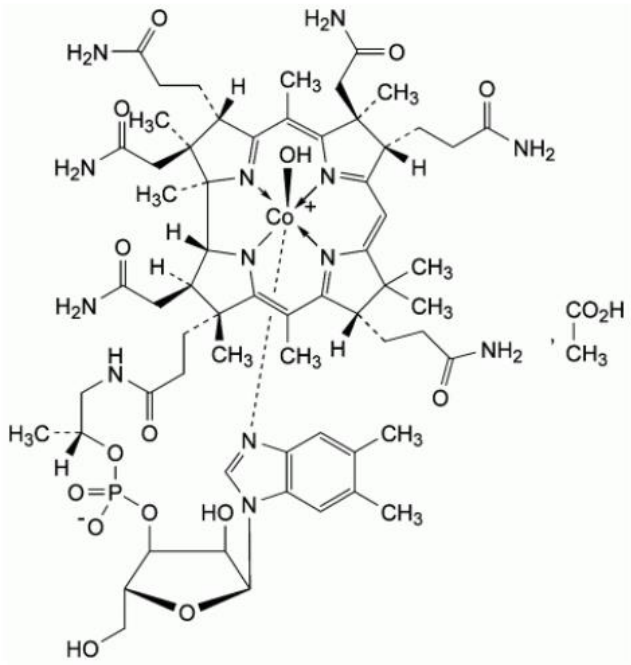
INN: Hydroxocobalamin acetate [rINNM (en)]

Chemical name: Coα-[α-(5,6-dimethylbenzimidazolyl)]-Coβ-hydroxocobamide acetate

Molecular formula: $C_{64}H_{93}CoN_{13}O_{17}$

Structure:

Structural Formula of Hydroxocobalamin acetate



Mr: 1406

Appearance: Dark red, crystalline powder or dark red crystals , very hygroscopic..

Solubility: Soluble in water

All aspects of the manufacture and control of the active substance, hydroxocobalamin acetate, 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 produce a solution of injection that could be used interchangeably with Neo-Cytamen 1000 microgams/ml solution for injection (PL 36301/001; RPH Pharmaceuticals AB). Suitable pharmaceutical development data have been provided for this application.

All excipients comply with their European Pharmacopoeia monograph and satisfactory Certificates of Analysis has been provided.

None of the excipients contain materials of animal or human origin.

This product does not contain or consist of genetically modified organisms (GMO).

Manufacturing Process

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 with full production-scale batches that have shown satisfactory results.

Control of Finished Product

The finished product specification is acceptable. Test methods have been described that have been validated adequately. Batch data complying with the release specification have been provided. 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 18 years, with the special storage conditions “Do not store above 25°C. Do not freeze. Store in the original package in order to protect from light” has been approved.

Bioequivalence/Bioavailability

A bioequivalence study was not necessary to support this application for an aqueous parenteral product.

II.4 Discussion on chemical, pharmaceutical and biological aspects

It is recommended that a Marketing Authorisation is granted for Hydroxocobalamin injection, from a quality point of view.

III NON-CLINICAL ASPECTS

III.1 Introduction

The pharmacodynamic, pharmacokinetic and toxicological properties of hydroxocobalamin are well-known.

The applicant’s non-clinical overview 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.3 Pharmacokinetics

No new data have been submitted and none are required for this type of application. Refer to Section III.1 Introduction, above.

III.4 Toxicology
No new data have been submitted and none are required for this type of application . Refer to Section III.1 Introduction, above.

III.5 Ecotoxicity/Environmental Risk Assessment (ERA)
Suitable justification has been provided for non-submission of an Environmental Risk Assessment. As the application is for substitution of an already authorised product, it is not expected that environmental exposure of hydroxocobalamin will increase following approval of the Marketing Authorisation for the proposed product. An environmental risk assessment is therefore not deemed necessary.

III.6 Discussion of the non-clinical aspects
No new non-clinical studies were conducted, which is acceptable given that the application was based on being a generic application of a reference product that has been licensed for over 10 years.

It is recommended that a Marketing Authorisation is granted, from a non-clinical point of view.

IV. CLINICAL ASPECTS
IV.1 Introduction
The clinical pharmacology of hydroxocobalamin is well-known. The clinical overview has been written by an appropriately qualified person and is a suitable summary of the clinical aspects of the dossier.

No new clinical pharmacology data have been submitted and none are required for an application of this type. A bioequivalence study was not necessary to support this application for a parenteral product. According to CHMP guidelines, bioequivalence studies are not generally required for aqueous parenteral solutions (CPMP/EWP/QWP/1401/98 Rev. 1/Corr**, guideline on the investigation of bioequivalence).

IV.2 Pharmacokinetics
The pharmacokinetic properties of hydroxocobalamin are well known and are adequately described in the applicant's clinical overview. No new pharmacokinetic data were submitted, and none are required for this type of application.

IV.3 Pharmacodynamics
The clinical pharmacodynamic properties of hydroxocobalamin are well-known. No new pharmacodynamic data were submitted and none are required for an application of this type.

IV.4 Clinical Efficacy
The clinical efficacy of hydroxocobalamin is well-known. No new efficacy data are presented or are required for this type of application.

IV.5 Clinical Safety
The safety profile of hydroxocobalamin is well known. No new safety data have been submitted with the application and none are required. No new or unexpected safety concerns arose from this application.

IV.6 Risk Management Plan
The applicant 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 injection.

A summary of safety concerns is listed in the table below:

Table: Summary of safety concerns

Summary of safety concerns	
Important identified risks	• **Irreversible neurological disturbances when applied to patients with folic acid deficiency** • **Hypersensitivity reactions** **Hypokalaemia**
Important potential risks	• **None**
Missing information	• **None**

Routine pharmacovigilance and risk minimisation measures are proposed. This is acceptable.

IV.7 Discussion of the clinical aspects

It is recommended that a Marketing Authorisation is granted, 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.

IV. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

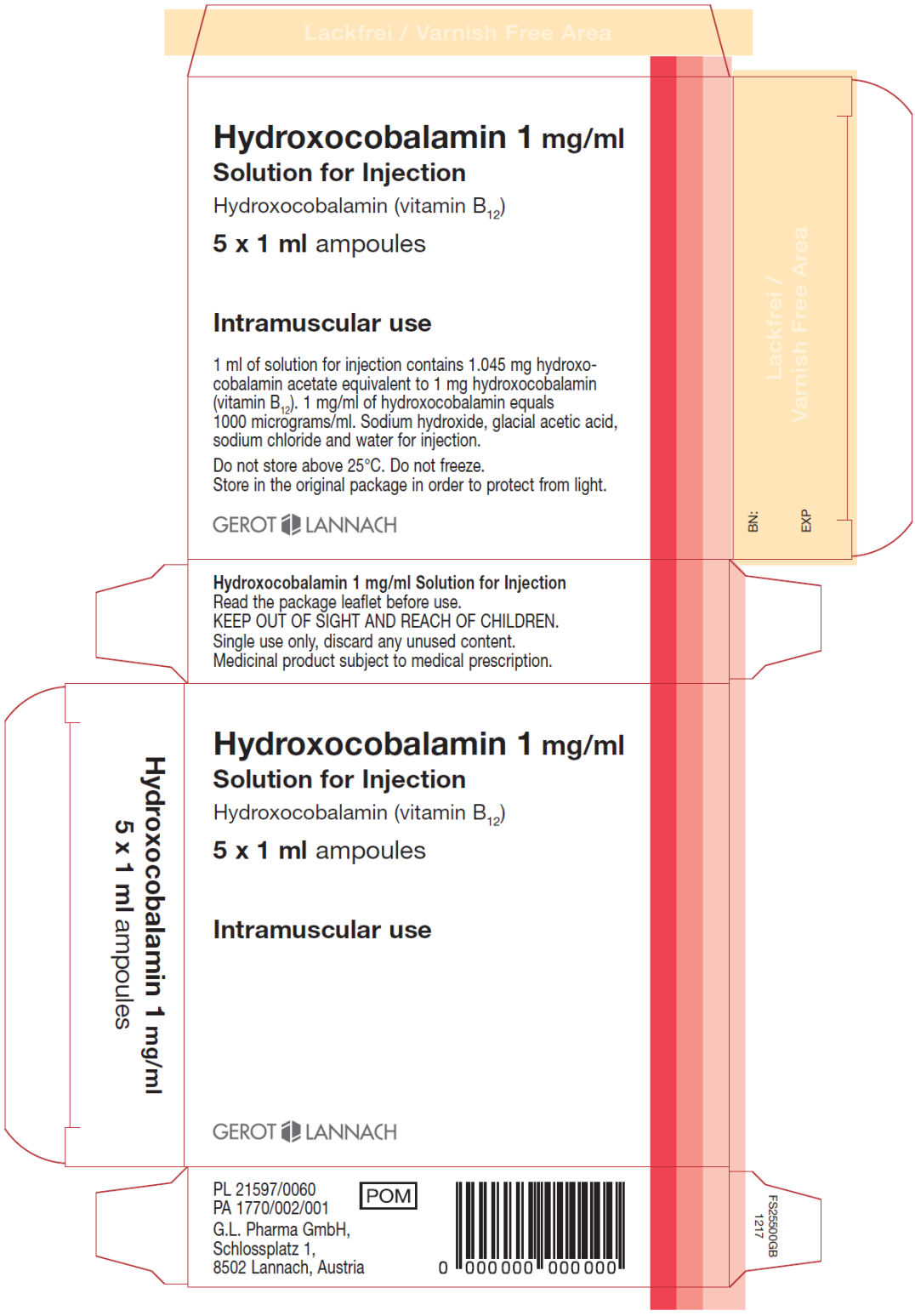
The quality of the product is acceptable, and no new non-clinical safety concerns have been identified. Extensive clinical experience with hydroxocobalamin in the proposed indications is considered to have demonstrated the therapeutic value of the compound. The proposed product is considered bioequivalent to the respective reference product.

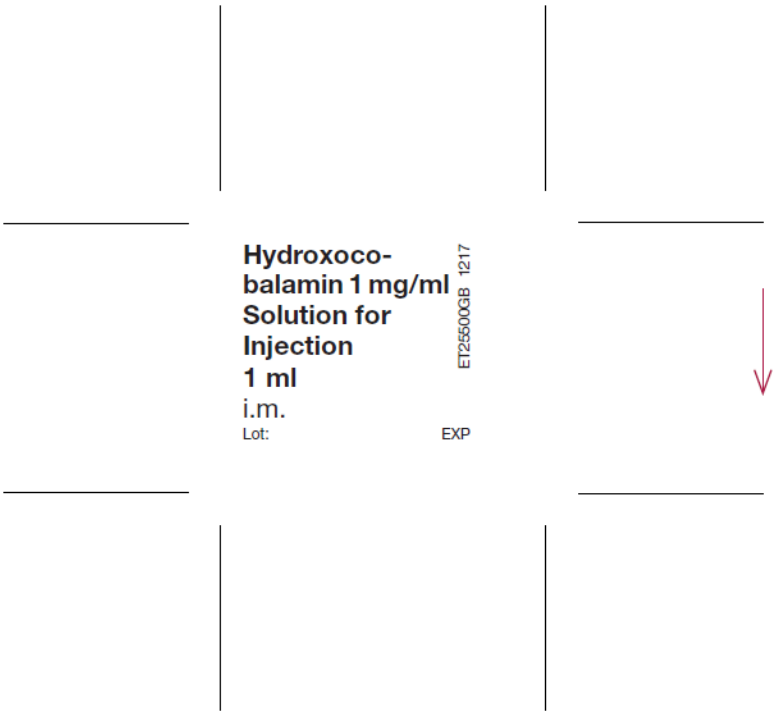
The overall benefit/risk balance is, therefore, considered to be positive.

The grant of a Marketing Authorisation is recommended.

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

The current labelling text is presented below.




Hydroxoco-
balamin 1 mg/ml
Solution for
Injection
1 ml
i.m.
Lot:
EXP
ET25500GB 1217

ANNEX 1-Table of content of the PAR update for MRP and DCP

Steps taken after the initial procedure with an influence on the Public Assessment Report

Scope	Procedure number	Product information affected	Date of start of the procedure	Date of end of procedure	Approval/ non approval	Assessment report attached Y/N (version)