

Public Assessment Report

Scientific discussion

Beriglobin

(human normal immunoglobulin)

Asp no: 2011-1339

This module reflects the scientific discussion for the approval of Beriglobin. The procedure was finalised at 2013-12-05. For information on changes after this date please refer to the module 'Update'.

I. INTRODUCTION

CSL Behring GmbH has applied for a marketing authorisation for Beriglobin, solution for injection in pre-filled syringe, 160 mg/ml. The active substance human normal immunoglobulin is the same as in Beriglobin, solution for injection, supplied in ampoules, marketed by CSL Behring GmbH, since 1987. This PAR only concerns Beriglobin, solution for injection in pre-filled syringe, 160 mg/ml. No PAR has been prepared for the previous approved product Beriglobin, solution for injection, 160 mg/ml. For approved indications, see the Summary of Product Characteristics.

II. QUALITY ASPECTS

II.1 Introduction

Beriglobin is presented in the form of a solution for injection containing 160 mg/ml human normal immunoglobulin. The excipients are glycine, sodium chloride, hydrochloric acid or sodium hydroxide (in small amounts for pH adjustment), and water for injections. The product is supplied in a graduated pre-filled syringe with 2 ml fill size. Beriglobin contains at least 100 IU/ml of antibodies against HAV and the indication applied for is the same as the currently approved product in ampoules, prophylaxis against hepatitis A infection. The product is administered by intramuscular injection.

II.2 Drug Substance

Human normal immunoglobulin is isolated from human plasma during the manufacture of the final product. Regarding the quality of the starting material, human plasma, the CSL Behring Plasma Master File (PMF) has been certified by EMA with the number EMEA/H/PMF/000001/04. The certified PMF covers the information about the measures put in place to prevent infections being passed on to patients from the starting material, such as careful selection of blood and plasma donors, testing of each donation and pools of plasma for signs of virus/infections.

II.3 Medicinal Product

Beriglobin, solution for injection in pre-filled syringe, 160 mg/ml is formulated using excipients described in the current Ph Eur.

The manufacturing process has been sufficiently described and critical steps identified. Results from the process validation studies confirm that the process is under control and ensure both batch to batch reproducibility and compliance with the product specification.

The tests and limits in the specification are in compliance with the European Pharmacopoeia monograph for Human Normal Immunoglobulin and are considered appropriate to control the quality of the finished product in relation to its intended purpose.

Stability studies under ICH conditions have been performed and data presented support the shelf life claimed in the SPC, when stored at 2-8°C.

With regard to measures taken to prevent transmission of infections resulting from the use of human blood or plasma no new data was provided for this application but reference can be given to the product supplied in ampoules marketed since 1987 using the same manufacturing process. Satisfactory reduction of viruses has been demonstrated for the production process. Effective reduction of enveloped viruses such as HIV, hepatitis B and hepatitis C has been shown as well as significant reduction of non-enveloped viruses such as hepatitis A virus. The process has shown limited efficacy in reducing the non-enveloped parvovirus B19 as this virus may be present in very high titres in human plasma. Therefore, it is stated in the SPC (under point 4.4) that the inactivation/elimination procedures may be of limited value against certain non-enveloped viruses such as parvovirus B19. There is however reassuring clinical experience regarding the lack of hepatitis A virus or parvovirus B19 transmission with immunoglobulins and it is also assumed that the antibody content makes an important contribution to the viral safety.

No material used in the manufacturing of Beriglobin originates from animal species susceptible to TSE.

The pre-filled syringe is graduated. To guarantee acceptable dosage accuracy down to 0.1 ml the company has included a recommendation in the labeling how to administrate low volumes. The graduation for volumes below 0.5 mL has been colored blue on the syringe. The SPC and PIL refers to the blue colored part of the graduation and states that a CE-marked adapter and a CE-marked small syringe is needed for correct dosing of volumes equal to or below 0.5 mL.

III. NON-CLINICAL ASPECTS

There is no new non-clinical information. This line extension concerns a new presentation with the same strength and indication as previously approved.

IV. CLINICAL ASPECTS

IV.1 Introduction

Beriglobin 160 mg/ml, solution for injection, supplied in ampoules (2 ml) has been licensed in Sweden since 1987. Beriglobin is a human normal immunoglobulin which contains at least 100 IU/ml of antibodies against hepatitis A virus. The indication applied for is the same as the currently approved product in ampoules, prophylaxis against hepatitis A infection.

A statement was provided to confirm that the Expert Report on clinical documentation for the product Beriglobin® P (dated September 23, 2002) reflects the current status of knowledge. Since September 23, 2002 no further clinical studies for Beriglobin ® P have been sponsored by CSL Behring.

IV.2 Clinical efficacy

Efficacy studies have been performed with predecessor preparations of the product. No efficacy studies with Beriglobin intramuscular (ImIg) administration have been performed.

ImIg substitution in patients with antibody deficiency has however been successfully used in this indication over decades. Subcutaneous (s.c.) substitution in patients with primary immunodeficiency with an ImIg has, however, been observed in patients which was well

tolerated even by patients who had a history of serious adverse reactions to previous intravenous (i.v.) or ImIgG administration.

In addition it is included in the European Core Summary of Product Characteristics (Core SPC) of the Committee for Proprietary Medicinal Products for human normal immunoglobulins i.m.

Prophylaxis of hepatitis A

In this indication, no studies have been performed with Beriglobin under the sponsor's supervision. The following noncompany sponsored clinical study is reported in the literature:

In a study (Ardjah,1992) were administered i.m. applications of 5 ml Beriglobin to a total of 334 travelers (among them 78 children / adolescents aged 8 - 18 years) to countries where hepatitis A was endemic. The injection was given 1 or 2 days before start of the travel. The injections were very well tolerated and no cases of hepatitis A were detectable after the travel.

Radiogenic mucositis

After a retrospective analysis the positive influence of ImIg on radiogenic mucositis was assessed in a prospective, randomized, placebo-controlled, double-blind study in 81 patients of either sex with malignant head and neck tumors with radiation therapy who had subsequently developed radiogenic mucositis.

Patients received i.m. injections either of preparation BER 008 (a predecessor of Beriglobin) or placebo (human albumin) on day 0 (10 ml), day 2 (5 ml) and day 4 (5 ml). Beyond day 7 open-label follow-up treatment with BER 008 was optional in both groups. The overall analysis showed a clearly significant treatment effect and the study medication was tolerated very well, as no adverse events of local or general type were reported.

A number of non-company sponsored studies report about their experiences on successful therapy with i.m. Beriglobin therapy in patients with radiogenic mucositis in the head and neck area after treatment of tumours or dermatitis of the thorax after surgical treatment of breast carcinoma. The patients reported beneficial short-term as well as long-term effects of the intramuscular Ig treatment. Overall a clinically beneficial influence of ImIg treatment was found.

A prospective study of the efficacy of prophylactic application of ImIg in patients with head and neck cancer who were given postoperative radiation treatment or combined radio-chemotherapy showed that the effect of ImIg was less significant than in other studies where ImIg had been given therapeutically.

IV.3 Clinical safety

The spontaneous reports are compared to the known safety profile of Beriglobin which includes allergic/anaphylactic, cardiovascular and generalized reactions. To reduce the risk of transmission of infective agents, stringent controls are applied to the selection of blood/plasma donors and donations. In addition, virus elimination/inactivation procedures are included in the production process of Beriglobin.

The presented clinical data do not raise any significant safety issues. No recent post marketing safety data have, however, been provided. The previous risk-benefit evaluation is considered favourable although no new evaluation of post marketing safety data is possible.

IV.4 Discussion on the clinical aspects

The proposed approach to improve the dosage accuracy for small doses is found acceptable. There are no objections to approval of Beriglobin 160 mg/ml, solution for injection in pre-filled syringe, from a non-clinical and clinical point of view.

The application is recommended for approval.

V. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

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 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 label and package leaflet of medicinal products for human use.

The risk/benefit ratio is considered positive and Beriglobin, solution for injection in pre-filled syringe, 160 mg/ml is recommended for approval.

VI. APPROVAL

Beriglobin, solution for injection in pre-filled syringe, 160 mg/ml was approved in the national procedure on 2013-12-05.

Public Assessment Report – Update

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)