1. NAME OF THE MEDICINAL PRODUCT

BERIGLOBIN® P

Solution for injection for subcutaneous or intramuscular administration

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active ingredient: Human normal Immunoglobulin.

1 ml contains:
Human protein 160 mg
Thereof immunoglobulins G at least 95%

Distribution of IgG subclasses:
IgG_1 ca. 61 %
IgG_2 ca. 28 %
IgG_3 ca. 5 %
IgG_4 ca. 6 %

IgA max. 1.7 mg

Antibodies to hepatitis A virus at least 100 I.U.

Excipient:
Sodium (as chloride and hydroxide): 0.8 to 1.6 mg/ml.
For a full list of excipients, see 6.1

3. PHARMACEUTICAL FORM
Solution for injection for subcutaneous or intramuscular administration.
Beriglobin P is a clear solution. The colour can vary from colourless to pale-yellow up to light brown during shelf life.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Substitution in
a) Primary antibody deficiency syndromes resulting from defective antibody synthesis.
b) Protracted transitory hypogammaglobulinaemia especially in premature infants

Prophylaxis of hepatitis A
- Before exposure
- Within 2 weeks after exposure

4.2 POSOLOGY AND METHOD OF ADMINISTRATION

Posology
The dosage and intervals of infusion are dependent on the indication.

Substitution in antibody deficiency syndrome

The product should be administered via the subcutaneous route.
The dosage may need to be individualised for each patient dependent on the pharmacokinetic and clinical response. The following dosage regimens are given as a guideline
The dosage regimen using the subcutaneous route should achieve a sustained plasma level of IgG. A loading dose of at least 0.2 to 0.5 g/kg (1.3 to 3.1 ml/kg) body weight - divided over several days with a maximal daily dose of 0.1 to 0.15 g/kg body weight and as indicated by the treating physician - may be required. After steady state IgG levels have been attained, maintenance doses are administered at repeated intervals, ideally weekly, to reach a cumulative monthly dose of about 0.4 to 0.8 g/kg (2.5 to 5 ml/kg) body weight.

Trough levels of IgG should be measured in order to adjust the dose and dosage interval.

Prophylaxis:
Hepatitis A prophylaxis
- Short-term prophylaxis in travelers who present less than 2 weeks before possible exposure:
  For stays in endemic areas of less than 3 months, a dose of 0.003 to 0.004 g/kg (0.02 ml/kg) body weight is recommended to be administered intramuscularly. Beriglobin P can be given in combination with Hepatitis A vaccine, but at different sites of the body.
- Hepatitis A prophylaxis in persons exposed less than 2 weeks previously: 0.003 to 0.004 g/kg (0.02 ml/kg) body weight administered intramuscularly

Method of Administration
Beriglobin P is already for use and should be administered at body temperature.
Do not use solutions which are cloudy or have deposits.
Depending on the indication, Beriglobin P should be administered via the subcutaneous or intramuscular route.

Subcutaneous administration
Subcutaneous infusion should be initiated and monitored by a physician experienced in the treatment of immunodeficiencies and in the guidance of patients for home treatment. The patient will be instructed in the use of syringe driver, infusion techniques, the keeping of a treatment diary and measures to be taken in case of severe adverse events. The recommended infusion rate is 22 ml/hour. In a clinical study with 53 patients evaluated, during the training phase under supervision of a physician, the infusion rate was increased from initially 10 ml to 22 ml/hour. The product should preferably be administered in the abdominal wall, thigh and/or buttocks. No more than 15 ml should be injected into a single site. Doses over 15 ml should be divided and injected into 2 or more sites.

Intramuscular administration
Intramuscular injection must be given by a physician or nurse.
Beriglobin P should preferably be administered ventrogluteally with the patient lying down.
If larger doses are required, it is advisable to administer them in divided fractions. This applies in the case of doses above 2 ml in children of up to 20 kg of body weight and doses above 5 ml for persons above 20 kg body weight.
Do not inject intravenously! Note that there is an increased risk of inadvertent intravascular injection in patients who have repeatedly received intramuscular injections.
See sections 3. “Pharmaceutical form” and 6.6 “Special precautions for disposal and other handling” for further information regarding method of administration.

4.3 CONTRAINDICATIONS
Hypersensitivity to any of the components of the product.
Do not inject intravascularly!
Beriglobin P must not be administered intramuscularly in cases of disorders of haemostasis.

4.4 Special warnings and precautions for use
Do not inject intravascularly! If Beriglobin P is accidentally administered into a blood vessel, patients could develop shock or thromboembolic events. When administering intramuscularly it is recommended to ensure by aspiration that no vessel has been penetrated.

The recommended infusion rate stated under section “4.2 Method of administration” should be adhered to.

Patients should be closely monitored and carefully observed for any adverse event throughout the infusion period.

Certain adverse reactions may occur more frequently in patients who receive human normal immunoglobulin for the first time or, in rare cases, when the product is switched or when treatment has been paused for more than eight weeks.

True hypersensitivity reactions are rare. They can occur in the very rare cases of IgA deficiency with anti-IgA antibodies and these patients should be treated with caution.

Rarely, Beriglobin P can induce a fall in blood pressure with anaphylactic reaction, even in patients who had tolerated previous treatment with normal human immunoglobulin.

Potential complications can often be avoided by ensuring that
- patients are not sensitive to human normal immunoglobulin by first injecting the product slowly (see also section 4.2 “Method of administration”);
- patients are carefully monitored for any symptoms throughout the infusion period. In particular, patients should be monitored during the first infusion and for the first hour thereafter, in order to detect potential adverse reactions in the following situations:
  – patients naïve to human normal immunoglobulin,
  – patients switched from an alternative product, or
  – when there has been a long interval since the previous infusion.

All other patients should be observed for at least 20 minutes after administration.

On suspicion of an allergic or anaphylactic reaction the administration has to be discontinued immediately. In case of shock the current medical standards for shock treatment have to be applied.

Thromboembolic Events associated with subcutaneous substitution therapy
The subcutaneous use of high doses of immunoglobulins for substitution therapy (e.g. primary immunodeficiency syndrome) have been associated with arterial and venous thromboembolic events including myocardial infarction, stroke, deep venous thrombosis and pulmonary embolism. Caution should be exercised in prescribing Beriglobin for subcutaneous substitution therapy in such patients with pre-existing risk factors for thrombotic events (such as advanced age, hypertension, diabetes mellitus and a history of vascular disease or thrombotic episodes, patients with acquired or inherited thrombophilic disorders, patients with prolonged periods of immobilization, severely hypovolemic patients, patients with diseases which increase blood viscosity). These patients should be informed about first symptoms of thromboembolic events including shortness of breath, pain and swelling of a limb, focal neurological deficits and chest pain and should be advised to contact their physician immediately upon onset of symptoms. Such patients should be sufficiently hydrated before use of Beriglobin.
Important information about some special excipients of Beriglobin P
This medicine contains up to 110 mg sodium per dose (body weight 75 kg) if the maximal daily dose (11.25 g = 70.3 ml) is applied. To be taken into consideration in patients on a controlled sodium diet.

Virus safety
Standard measures to prevent infections resulting from the use of medicinal products prepared from human blood or plasma include selection of donors, screening of individual donations and plasma pools for specific markers of infection and the inclusion of effective manufacturing steps for the inactivation/removal of viruses. Despite this, when medicinal products prepared from human blood

or plasma are administered, the possibility of transmitting infective agents cannot be totally excluded. This also applies to unknown or emerging viruses and other pathogens.

The measures taken are considered effective for enveloped viruses such as HIV, HBV and HCV, and for the non-enveloped viruses HAV and parvovirus B19.

There is reassuring clinical experience regarding the lack of hepatitis A or parvovirus B19 transmission with immunoglobulins and it is also assumed that the antibody content makes an important contribution to the virus safety.

In the interest of patients, it is strongly recommended that every time that Beriglobin P is administered to them, the name and batch number of the product are recorded in order to maintain a link between the patient and the batch of the product.

4.5 Interactions with other medicinal products and other forms of interactions

Live attenuated virus vaccines

Immunoglobulin administration may impair for a period of at least six weeks and up to three months the efficacy of live attenuated virus vaccines such as measles, rubella, mumps, and varicella vaccines. After administration of Beriglobin P, an interval of at least three months should elapse before vaccination with live attenuated virus vaccines.
In the case of measles, this impairment may persist for up to one year. Therefore patients receiving measles vaccine should have their antibody status checked.

Interference with serological testing
It has to be considered that when serological test results are interpreted, the transitory rise of passively transferred antibodies after immunoglobulin injection may result in misleading positive test results.
Passive transmission of antibodies to erythrocyte antigens, e.g., A, B and D, may interfere with some serological tests for red cell allo-antibodies (e.g. Coombs test).

4.6 Pregnancy and lactation
There are no controlled clinical trials on the use in human pregnancy. Therefore, the administration of this medicinal product to pregnant women or breast-feeding mothers should be carefully considered. Clinical experience with immunoglobulins suggests that no harmful effects on the course of pregnancy or on the foetus and the neonate are to be expected.

4.7 Effects on ability to drive and use machines
There are no indications that Beriglobin P may impair the ability to drive or use machines.

4.8 Undesirable effects
In a clinical study with s.c. administration in 60 patients the following undesirable effects have been reported.
The following standard categories of frequency are used:

Very common	≥ 1/10
Common	≥ 1/100 and < 1/10
Uncommon	≥ 1/1,000 and < 1/100
Rare	≥ 1/10,000 and < 1/1,000
Very rare	< 1/10,000 (including reported single cases)

- ***Local reactions at the injection/infusion site***

  Very common: swelling, soreness, redness, induration, local heat, itching, bruising or rash.

  The frequency declined very rapidly within the first ten infusions, when patients became used to the subcutaneous form of treatment. (In study patients who were treated with subcutaneous immunoglobulin for years before the trial, injection site reactions were not reported.)

- ***Immune system disorders***
  In single cases: Allergic reactions including fall in blood pressure

- ***General disorders***
  In single cases: Generalized reactions such as chills, fever, headache, malaise, moderate back pain, syncope, dizziness, rash, bronchospasm.

  Adverse reactions reported from post marketing surveillance are similar to the reactions which have also been observed during the clinical trials. In addition, the following have also been reported during post marketing surveillance:

- ***Immune system disorders***
  Allergic/anaphylactic reactions including dyspnoea, cutaneous reactions, in isolated cases reaching as far as anaphylactic shock, even when the patient has shown no hypersensitivity to previous administration

- ***General disorders***
  Generalized reactions such as nausea, vomiting, arthralgia

- ***Cardiovascular disorders***
  Cardiovascular reactions particularly if the product has been inadvertently injected intravascularly.

- ***Vascular disorders associated with subcutaneous substitution therapy***
  There are reports from patients being treated subcutaneously with high doses of immunoglobulins for substitution therapy (e.g. primary immunodeficiency syndrome) of arterial and venous thromboembolic events including myocardial infarction, stroke, deep venous thrombosis and pulmonary embolism.

For information on infectious disease risk see section 4.4. subheading “Virus safety”

4.9 Overdose
Consequences of an overdose are not known.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties
Pharmacotherapeutic group: immune sera and immunoglobulins, immunoglobulins, normal human for extravascular administration.
ATC code: J06B A01

Normal human immunoglobulin contains mainly immunoglobulin G (IgG) having a broad spectrum of antibodies against various infectious agents.

Beriglobin P contains the immunoglobulin G antibodies present in the healthy population. It is usually prepared from pooled plasma of at least 1,000 donors. It has a distribution of immunoglobulin G subclasses closely proportional to that in native human plasma. Adequate doses of this medicinal product may restore abnormally low immunoglobulin G levels to the normal range.

5.2 Pharmacokinetic properties
With subcutaneous administration of human normal immunoglobulin, peak levels are achieved in the recipient’s circulation after approximately 2 days.
Data from a clinical study (n=60) show that trough levels of approximately 8 to 9 g/l (n=53) in the plasma can be maintained by weekly doses between 0.05 and 0.15 g (0.3 to 0.9 ml) Beriglobin P per kg body weight. This is commensurate to a monthly cumulative dosage of 0.2 to 0.6 g per kg body weight.
With intramuscular administration Beriglobin P is bioavailable in the recipient’s circulation after a delay of approximately 2 to 3 days

IgG and IgG-complexes are broken down in cells of the reticuloendothelial system.

5.3 Preclinical safety data
There are no preclinical data considered relevant to clinical safety beyond data included in other sections of the SPC.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Aminoacetic acid (glycine), sodium chloride, hydrochloric acid or sodium hydroxide (in small amounts for pH adjustment), water for injections

6.2 Incompatibilities
In the absence of compatibility studies this medicinal product must not be mixed with other medicinal products, solvents or diluents.

6.3 Shelf life
30 months

Beriglobin P must not be used after the expiry date given on the pack and container.
Once the container has been opened its contents are to be used immediately.

6.4 Special precautions for storage
Store in a refrigerator (+2°C to +8°C) in the outer carton in order to protect from light. Do not freeze!
Keep out of the reach and sight of children!

6.5 Nature and contents of container
Presentations
Pack with 1 ampoule of 2 ml
Pack with 1 prefilled syringe of 2 ml
Pack with 1 ampoule of 5 ml
Pack with 1 prefilled syringe of 5 ml
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling
Beriglobin P is a ready-for use solution and should be administered at body temperature.
Do not use solutions that are cloudy or have deposits. The product must be inspected visually prior to administration and should not be used if there is any variation of physical appearance (see also section 3. “Pharmaceutical form”).

Any unused product or waste material should be disposed of in accordance with local requirements.

7. MANUFACTURER
CSL Behring GmbH
Emil-von-Behring-Str. 76
35041 Marburg, Germany

8. REGISTRATION HOLDER
Genmedix, 12 Beit Harishonim St. Emek-Hefer 38777

9. REGISTRATION NUMBER: 125 38 29064

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