BERIGLOBIN P

1. NAME OF THE MEDICINAL PRODUCT

Beriglobin® P
Solution for injection for subcutaneous or intramuscular administration

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Human normal immunoglobulin

One ml contains:
Human normal immunoglobulin 160 mg
(of which at least 95 % IgG)

Each prefilled syringe of 2 ml contains: 320 mg of human normal immunoglobulin.
Each prefilled syringe of 5 ml contains 800 mg of human normal immunoglobulin.

Antibodies to hepatitis A virus at least 100 IU/ml

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

The maximum IgA content is 1700 micrograms/ml.

Produced from the plasma of human donors.

Excipients with known effects:
Sodium (as chloride and hydroxide): 0.8 to 1.6 mg/ml.

For the 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
- Primary antibody deficiency syndromes resulting from defective antibody synthesis.
- 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 ready 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 the active substance or to any of the excipients listed in section 6.1 (see section 4.4).
Beriglobin P must not be given intravascularly.

It must also not be administered intramuscularly in cases of severe thrombocytopenia and in other disorders of haemostasis.

4.4 Special warnings and precautions for use

If Beriglobin P is accidentally administered into a blood vessel, patients could develop shock.

The recommended infusion rate given under section 4.2 must be closely followed. Patients should be closely monitored and carefully observed for any adverse reaction 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 human normal immunoglobulin product is switched or when it is not administered in regular intervals.

Potential complications associated with subcutaneous administration can often be avoided by:

- initially injecting the product slowly (10 ml/hr), see also section 4.2 “Posology and method of administration”;
  - ensuring that patients are carefully monitored for any adverse reaction throughout the infusion period. In particular, patients naïve to human normal immunoglobulin, patients switched from an alternative product or when it is not administered in regular intervals should be monitored during the first infusion and for the first hour after the first infusion, in order to detect potential adverse signs.

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. The treatment required depends on the nature and severity of the adverse reaction.
In case of shock, standard medical treatment for shock should be implemented.

Hypersensitivity

True allergic reactions are rare. They can particularly occur in patients with anti-IgA antibodies who should be treated with particular caution. Patients with anti-IgA antibodies, in whom treatment with subcutaneous IgG products remains the only option, should be treated with Beriglobin P only under close medical supervision.
Rarely and for unknown reasons, human normal immunoglobulin can induce a fall in blood pressure with anaphylactic reaction, even in patients who had tolerated previous treatment with human normal immunoglobulin.

Thromboembolism

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. Patients should be sufficiently hydrated before use of immunoglobulins. Caution should be exercised in patients with preexisting 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).

Patients should be informed about first symptoms of thromboembolic events including unexplained cough, 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.

Aseptic Meningitis Syndrome (AMS)

Aseptic meningitis syndrome has been reported to occur in association with subcutaneous immunoglobulin treatment; the symptoms usually begin within several hours to 2 days following treatment. Discontinuation of immunoglobulin treatment may result in remission of AMS within several days without sequelae.

Patients should be informed about first symptoms which encompass severe headache, neck stiffness, drowsiness, fever, photophobia, nausea, and vomiting.

Important information about some of the ingredients of Beriglobin P

This medicine contains up to 110 mg (4.78 mmol) sodium per dose (body weight 75 kg) if the maximal daily dose (11.25 g = 70.3 ml) is applied. This should be taken into consideration in patients on a controlled sodium diet.

Interference with serological testing

After injection of immunoglobulin the transitory rise of the various passively transferred antibodies in the patient's blood may result in misleading positive results in serological testing.
Passive transmission of antibodies to erythrocyte antigens, e.g. A, B, D may interfere with some serological tests for red cell antibodies for example the direct antiglobulin test (DAT, direct Coombs' test).

Transmissible agents

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 human immunodeficiency virus (HIV), hepatitis B virus (HBV) and hepatitis C virus (HCV), and for the non-enveloped hepatitis A (HAV) and parvovirus B19 viruses.

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.

Paediatric population

The listed warnings and precautions apply both to adults and children.

4.5 Interactions with other medicinal products and other forms of interaction

Live attenuated virus vaccines

Immunoglobulin administration may impair for a period of at least 6 weeks and up to 3 months the efficacy of live attenuated virus vaccines such as measles, rubella, mumps and varicella. After administration of this medicinal product, an interval of 3 months should elapse before vaccination with live attenuated virus vaccines. In the case of measles, this impairment may persist for up to 1 year. Therefore patients receiving measles vaccine should have their antibody status checked.

Paediatric population

The listed interactions apply both to adults and children.

4.6 Fertility, pregnancy and lactation

Pregnancy

The safety of this medicinal product for use in human pregnancy has not been established in controlled clinical trials and therefore should only be given with caution to pregnant women and breast-feeding mothers. Immunoglobulin products have been shown to cross the placenta, increasingly during the third trimester. 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.

Breast-feeding

Immunoglobulins are excreted into the milk and may contribute to protecting the neonate from pathogens which have a mucosal portal of entry.

Fertility

Clinical experience with immunoglobulins suggests that no harmful effects on fertility are to be expected.

4.7 Effects on ability to drive and use machines

The ability to drive and operate machines may be impaired by some adverse reactions associated with Beriglobin P. Patients who experience adverse reactions during treatment

should wait for these to resolve before driving or operating machines.

4.8 Undesirable effects

Summary of the safety profile

Adverse reactions such as chills, headache, dizziness, pyrexia, vomiting, hypersensitivity, nausea, arthralgia, hypotension and moderate low back pain may occur occasionally.

Rarely human normal immunoglobulins may cause a sudden blood pressure decrease and, in isolated cases, anaphylactic shock, even when the patient has shown no hypersensitivity to previous administration.

Local reactions at infusion sites: swelling, pain, erythema, induration, warmth, itching, bruising and rash, may frequently occur.

For information on infectious disease risk see section 4.4. subheading “Transmissible agents”.

Tabulated list of adverse reactions

Adverse reactions have been collected from clinical studies and post-marketing experience. The table presented below is according to the MedDRA system organ classification (SOC and Preferred Term Level).

Frequencies have been evaluated according to the following convention: Very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000), not known (cannot be estimated from the available data).

A frequency category has been applied to adverse reactions observed in clinical trials. However for adverse reactions received from post-marketing experience, it is not always possible to reliably estimate frequency since reporting is voluntary and from a population of an uncertain size. For these reactions ‘not known’ has been assigned.

Frequency of Adverse Reactions (ADRs) with Beriglobin P

MedDRA System Organ Class (SOC)	Adverse Reaction	Frequency	
		s.c. administration	i.m. administration
Immune system disorders	Hypersensitivity (including blood pressure decrease)	Common‡	Not known
	Anaphylactic shock/anaphylactic reactions (including dyspnoea, skin reaction)	Not known	Not known
Nervous system	Headache	Common‡	Common‡
	Syncope, dizziness	Common‡	Not known
Cardiac disorders	Cardiovascular disorder¶	Not known	Not known
Vascular disorders	Thromboembolism (including myocardial infarction, ischaemic stroke, deep venous thrombosis and pulmonary embolism) ^	Not known	(---)
Respiratory, thoracic and mediastinal disorders	Bronchospasm	Common‡	Not known
Gastrointestinal disorders	Nausea, vomiting	Not known	Not known
Skin and subcutaneous tissue disorders	Rash	Common‡	Not known
Musculoskeletal and connecitve tissue disorders	Back pain§	Common‡	Not known
General disorders and administration site conditions	Injections site pain§	Very common	Very common
	Injection site swelling, erythema, induration, warmth, pruritus, bruising, rash§	Very common	Not known
	Injection site urticaria†	(---)	Not known
	Pyrexia	Common‡	Common‡
	Chills, malaise	Common‡	Not known
	Arthralgia	Not known	Not known

‡Reported in single cases from clinical study.
¶Cardiovascular disorder particularly if the product has been inadvertently injected intravascularly.
^ Thromboembolism (including myocardial infarction, ischaemic stroke, deep venous thrombosis and pulmonary embolism) has been observed in association with s.c. substitution therapy only.
§In a clinical study with s.c. administration frequency of local reactions at the injection site (including pain, swelling, erythema, warmth, pruritus, bruising, rash) declined very rapidly with the first ten infusions, when patients became used to the s.c. form of treatment.
†Injection site urticaria has been observed with i.m. administration only.

Description of selected adverse reactions

Injection site urticaria has been observed with i.m. administration only.

Thromboembolism (including myocardial infarction, ischaemic stroke, deep venous thrombosis and pulmonary embolism) has been observed in association with s.c. substitution therapy only.

Paediatric population

Frequency, type and severity of adverse reactions in children are expected to be the same as in adults.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form
https://sideeffects.health.gov.il
and emailed to the Registration Holder's Patient Safety Unit at:
drugsafety@neopharmgroup.com

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

Human normal immunoglobulin contains mainly immunoglobulin G (IgG) with a broad spectrum of antibodies against various infectious agents.

Human normal immunoglobulin contains the IgG antibodies present in the normal population. It is usually prepared from pooled plasma from not fewer than 1000 donations. 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.

Beriglobin provides passive transfer of hepatitis A antibodies.

The mechanism of action in indications other than replacement therapy and hepatitis A prophylaxis is not fully elucidated, but includes immunomodulatory effects.

Paediatric population
No differences were seen in the pharmacodynamics properties between adult and paediatric study patients.

5.2 Pharmacokinetic properties

Following subcutaneous administration of Beriglobin P, peak serum levels are achieved after approximately 2 days.

In a clinical trial with Beriglobin P (n=52), the subjects achieved sustained trough levels (mean 9.3 g/l) over a period of 27 weeks when receiving median weekly doses of approximately 0.1 g/kg.IgG and IgG-complexes are broken down in cells of the reticuloendothelial system.

Paediatric population
No differences were seen in the pharmacokinetic parameters between adult and paediatric study patients.

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.

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.

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 °) in the outer carton in order to protect from light. Do not freeze!
Keep out of the sight and reach of children!

6.5 Nature and contents of container

Immediate containers
prefilled SCF syringes of colourless glass (Type I)

Presentations
Pack with 1 prefilled syringe of 2 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.
The medicinal product should be brought to room or body temperature before use.
The product should be inspected visually for particulate matter and discoloration prior to administration.
Solutions that are cloudy or have deposits should not be used.
Any unused product or waste material should be disposed of in accordance with local requirements.

7. MANUFACTURER

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Emil-von-Behring-Str. 76
35041 Marburg
Germany

8. REGISTRATION HOLDER

Genmedix,
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9. REGISTRATION NUMBER

125-38-29064

10. PRESCRIPTION STATUS

subject to medical prescription

Revised in October 2022 according to MoH guidelines.