SCHEDULING STATUS S4

1. NAME OF THE MEDICINE

BERIGLOBIN® P 2 ml Solution for Injection for subcutaneous or intramuscular administration

BERIGLOBIN® P 5 ml Solution for Injection for subcutaneous or intramuscular administration

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Human normal immunoglobulin (SCIg and IMIg)

One ml contains:

Human normal immunoglobulin 160,0 mg (purity of at least 95 %)

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 1 700 micrograms/ml.

Produced from the plasma of human donors.

For full list of excipients, see section 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

Indications for subcutaneous administration (SCIg)

Replacement therapy in adults, children and adolescents (0-18 years) in:

- Primary immunodeficiency syndromes with impaired antibody production (see section 4.4).
- Hypogammaglobulinaemia and recurrent bacterial infections in patients with chronic lymphocytic leukaemia (CLL), in whom prophylactic antibiotics have failed or are contraindicated.
- Hypogammaglobulinaemia and recurrent bacterial infections in multiple myeloma (MM) patients.
- Hypogammaglobulinaemia in patients pre- and post- allogeneic haematopoietic stem cell transplantation (HSCT).

Indications for intramuscular administration (IMIg)

Hepatitis A prophylaxis

In adults and children and adolescents (0-18 years)

- Pre-exposure prophylaxis, preferably in combination with vaccination, in unvaccinated individuals travelling in less than 2 weeks to areas of hepatitis A risk.
- Post-exposure prophylaxis in unvaccinated individuals within 2 weeks of hepatitis A virus (HAV) exposure.

Consideration should also be given to other official guidance on the appropriate use in hepatitis A prophylaxis.

For long term hepatitis A prophylaxis, vaccination is recommended.

Therapy of radiogenic mucositis

4.2 Posology and method of administration

Replacement therapy should be initiated and monitored under the supervision of a physician experienced in the treatment of immunodeficiency.

Posology

The dose and dose regimen are dependent on the indication.

Replacement therapy

The medicine should be administered via the subcutaneous route.

In replacement therapy the dose 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 dose regimen should achieve a trough level of IgG (measured before the next infusion) of at least 5 to 6 g/l and aim to be within the reference interval of serum IgG for age. A loading dose of at least 0,2 to 0,5 g/kg (1,3 to 3,1 ml/kg) body weight may be required. This may need to be divided over several days, with a maximal daily dose of 0,1 to 0,15 g/kg.

After steady state IgG levels have been attained, maintenance doses are administered at repeated intervals (approximately once per week) to reach a cumulative monthly dose of the order of 0,4 to 0,8 g/kg. Each single dose may need to be injected at different anatomic sites.

Trough levels should be measured and assessed in conjunction with the incidence of infection. To reduce the rate of infection, it may be necessary to increase the dose and aim for higher trough levels.

Hepatitis A prophylaxis

The medicine is to be administered via the intramuscular route.

To achieve a minimum protective level of 10 mIU/ml with an IMIg with a minimum antibody content for HAV of 100 IU/ml, the following dose is recommended:

- Pre-exposure prophylaxis in unvaccinated individuals travelling in less than 2 weeks to areas of hepatitis A risk (short term prophylaxis):
  For stays in endemic areas of less than 3 months: 0,17 ml/kg body weight (preferably given in combination with vaccination).
- Post-exposure prophylaxis in unvaccinated individuals within 2 weeks of exposure:
  0,17 ml/kg body weight.

Therapy of radiogenic mucositis

The medicine is to be administered via the intramuscular route.

Initially 10 ml (1600 mg), after 2 days 5 ml (800 mg) and after a further 2 days again 5 ml (800 mg). The treatment can be repeated as often as necessary.

Paediatric population

The posology in children and adolescents (0-18 years) is not different to that of adults as the posology for each indication is given by body weight and adjusted to the clinical outcome in replacement therapy indications.

Method of administration

For subcutaneous use

Subcutaneous infusion for home treatment should be initiated and monitored by a physician experienced in the guidance of patients for home treatment. The patient must be instructed in the use of a syringe driver, the infusion techniques and the keeping of a treatment diary. The patient must also be instructed in the recognition of and measures to be taken in case of severe adverse reactions.

Beriglobin P may be injected into sites such as abdomen, thigh, upper arm and lateral hip. It is recommended to use an initial administration speed of 10 ml/h/injection site. If well tolerated (see section 4.4), the infusion speed can be increased gradually every subsequent infusion. The recommended maximum speed is 22 ml/h/injection site. More than one injection

site can be used simultaneously. The amount of medicine infused into a particular site varies. In infants and children, infusion site may be changed every 5-15 ml. In adults doses over 30 ml may be divided according to patient preference. There is no limit to the number of infusion sites.

For intramuscular use

Intramuscular injection must be given by physician or nurse.

Do not inject intravascularly! Note that there is an increased risk of inadvertent intravascular injection in patients who have repeatedly received intramuscular injections.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed under section 6.1.

Beriglobin P must not be given intravascularly (see section 4.4).

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

Do not inject intravascularly!

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 medicine is switched or when it is not administered in regular intervals.

Potential complications can often be avoided by:

• initially injecting the medicine slowly (10 ml/hr), see also section 4.2;

– 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 immunoglobulin medicine 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 medicines remains the only option, should be treated with Beriglobin P only under close medical supervision.

Rarely, 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

Arterial and venous thromboembolic events including myocardial infarction, stroke, deep venous thrombosis and pulmonary embolism have been associated with the use of immunoglobulins. Patients should be sufficiently hydrated before use of immunoglobulins. Caution should be exercised in 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).

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 medicines 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 medicines 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.
It is strongly recommended that every time that BERIGLOBIN P is administered, the name and batch number is recorded in order to maintain a link between the patient and the batch of the medicine.

Paediatric population

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

4.5 Interaction with other medicines 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 BERIGLOBIN P, 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 BERIGLOBIN P for use in pregnancy has not been established in controlled clinical trials and therefore should only be given with caution to pregnant women and breastfeeding mothers. Immunoglobulin medicines 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.

Breastfeeding

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.

MedDRA System Organ Class (SOC)	**Adverse Reaction**	**Frequency**	
		Subcutanous administration	**Intramuscular 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 disorders	Headache	Common‡	Common‡
	Syncope, dizziness	Common‡	Not known
Cardiac disorders	Cardiovascular disorders¶	Not known	Not known
Vascular disorders	Thromboembolism (including	Not known	(---)

	myocardial infarction, ischaemic stroke, deep venous thrombosis and pulmonary embolism)[ǁ]		
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 medicine has been inadvertently injected intravascularly.

[ǁ] 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 medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare providers are asked to report any suspected adverse reactions to SAHPRA via the **"6.04 Adverse Drug Reaction Reporting Form"**, found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8.

In addition suspected adverse reactions can be reported to Gen-Eye (Pty) Ltd via email: pharmacovigilance@gen-eye.co.za or telephonically on 011 312 3812.

4.9 Overdose

Consequences of an overdose are not known.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

A 30.1 Biologicals – Antibodies

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 1 000 donations. It has a distribution of immunoglobulin G subclasses closely proportional to that in native human plasma. Adequate doses of this medicine 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.

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 BERIGLOBIN P must not be mixed with other medicines.

6.3 Shelf life

30 months

6.4 Special precautions for storage

Store in a refrigerator 2 ºC to 8 ºC in the outer carton in order to protect from light. Do not freeze!

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.

KEEP OUT OF REACH OF CHILDREN.

6.5 Nature and contents of container

BERIGLOBIN P 2 ml: A single dose 2 ml pre-filled syringe packed into a carton.

BERIGLOBIN P 5 ml: A single dose 5 ml pre-filled syringe packed into a carton.

6.6 Special precautions for disposal and other handling

Beriglobin P is a ready-for use solution.

It should be brought to room or body temperature before use.

It 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 medicine or waste material should be disposed of in accordance with local requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Gen-Eye (Pty) Ltd[1]

Royal Palm Business Estate

Unit 7, 646 Washington Street

Halfway House, Midrand, 1685

8. REGISTRATION NUMBER(S)

BERIGLOBIN P 2 ml: T/30.2/608

11/30.2/0037 (Namibia)

BERIGLOBIN P 5 ml: T/30.2/609

11/30.2/0038 (Namibia)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

The date on the registration certificate of BERIGLOBIN P: 09 September 1992

10. DATE OF REVISION OF THE TEXT

13 October 2023

BERIGLOBIN® P is a registered trademark of CSL Behring GmbH

[1] Company Registration number: 2009/009360/07

BER/PI/03/10.2023