COMPANY CORE DATA SHEET – CCDS

PRODUCT NAME: BERIRAB P

INN NAME: HUMAN RABIES IMMUNOGLOBULIN

VERSION: 4.0

REVISION DATE: 28-AUG-2024

PURPOSE: IgA limit.

Text Convention:	
Grey-shaded text:	**Mandatory text** in terms of content, emphasis and meaning
Normal font-text:	Recommended text
Italic blue font-text:	*Contains explanatory notes, instructions or definition not to be implemented into any labelling*

1. PRODUCT NAME

Berirab P

Solution for injection for intramuscular and /or intralesional use.

2. PHARMACEUTICAL INFORMATION

Active substance:

Human rabies immunoglobulin*

One ml solution contains 100 - 170 mg human plasma protein (purity of at least 95% immunoglobulin) with antibodies to rabies virus of at least 150 IU.

Each pre-filled syringe of 2 ml solution contains: at least 300 IU of rabies antibodies.
Each pre-filled syringe of 5 ml solution contains: at least 750 IU of rabies antibodies.

The maximum immunoglobulin type A (IgA) content is 3 mg/ml.

*Produced from the plasma of human donors.

Excipients with known effect:

Glycine, sodium chloride, water for injections

Berirab P contains 2-4 mg/ml sodium chloride.[1]

Berirab P contains no preservatives.

3. PHARMACEUTICAL FORM

Solution for injection for intramuscular and / or intralesional use.

Berirab 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 Indications

Post-exposure prophylaxis of rabies infection after:

- exposure to scratches, bites or other injuries caused by a suspected rabid animal[2]
- mucous membrane contamination with infectious tissue or saliva of a suspected rabid animal[2]
- contact of mucous membranes or newly skin injury with rabies live attenuated vaccine e.g. vaccination baits.[4]

Berirab P must always be used in combination with a rabies vaccine.[1,3]

Consideration should also be given to WHO guidelines and other official guidance regarding the use of human rabies immunoglobulin.[2,3]

4.2 Posology and method of administration

Posology

Post-exposure prophylaxis consists of a regimen of one dose of immunoglobulin and a full course of rabies vaccination.[3]

Berirab P and the first dose of rabies vaccine should be given as soon as possible after exposure. However, if not available immediately, Berirab P should be administered at any time up to and including 7 days after the first dose of vaccine.[4] Additional doses of rabies vaccine should be given according to official guidelines[3,4] or the manufacturer's instruction.

Rabies post-exposure prophylaxis exclusively with simultaneous vaccination:
recommended dose of rabies immunoglobulin is 20 IU Berirab P per kg body weight (bw).[2,4]

Because of the risk of interference with antibody production related to vaccination, neither the Berirab P dose should be increased nor repeat rabies immunoglobulin be given even if the onset of the simultaneous post-exposure prophylaxis is delayed.[2]

Consideration should also be given to WHO guidelines and other official guidance regarding posology and method of administration of human rabies immunoglobulin.[2]

Method of administration

For intramuscular and / or intralesional use.

Berirab P should be administered via the intramuscular and / or intralesional route.[2,7]

Of the total quantity of the Berirab P dose, as much as possible should be instilled deeply into and around the wound. The remaining amount of the calculated dose, if administered to the patient, should be injected intramuscularly at a site distant from the site of active vaccine administration.[2,4,5,6]

If comparatively large total volumes of Berirab P are required, it is advisable to administer them in divided doses at different sites. This applies in the case of doses above 2 ml for children up to 20 kg bw and doses above 5 ml for persons above 20 kg bw.[2]

In case of simultaneous post-exposure prophylaxis, Berirab P and the vaccine should be administered at contralateral sides of the body.[2]

The post-exposure prophylaxis should be carried out immediately also in the case when it is not known if the animal was infected with rabies virus.[3,4]

Suturing should be postponed if possible.[3,4] If required, wounds should be loosely sutured only after Berirab P infiltration into the wound.[2] All bite wounds and scratches are to be immediately washed and flushed with soap or detergent and copious water for 15 minutes.[3,4] An iodine- containing or another substance with virucidal activity should be applied to the wound.[3,4]

The above wound care instructions also apply for contamination with rabies live-attenuated vaccine, e.g. from a vaccination bait.[4]

In the presence of a coagulation disorder, in the case of which intramuscular injections are contraindicated, Berirab P may be given subcutaneously.[2] Afterwards the injection site should be compressed with a swab.[4] However, it should be noted that there are no clinical efficacy data to support administration by the subcutaneous route.[2]

For further instructions, see section 6.5.

4.3 Contraindications

Because of the life-threatening risk due to rabies, there are no contraindications to the administration of Berirab P.

4.4 Warnings and precautions

Hypersensitivity

Berirab P must not be injected intravascularly!

It must be ensured that Berirab P is not administered into a blood vessel because of the risk of shock.

True hypersensitivity reactions are rare. Berirab P contains a small quantity of Immunoglobulin A (IgA). Individuals who are deficient in IgA have the potential for developing IgA antibodies and may have anaphylactic reactions after administration of blood components containing IgA.

Rarely, Berirab P can induce a fall in blood pressure with anaphylactic reactions, even in patients who had tolerated previous treatment with human immunoglobulin.
Therapeutic measures depend on the nature and severity of the event. The current medical standards for shock treatment are to be observed.

Patients should be observed for at least 20 minutes after administration of Berirab P.
Particularly in cases of inadvertent intravenous injection, patients should be observed for longer term (at least 1 hour) after administration.

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

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

It is strongly recommended that every time that Berirab P is administered to a patient, 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

Vaccinations with live attenuated virus vaccines

Immunoglobulin administration may impair the efficacy of live attenuated virus vaccines such as measles, rubella, mumps and varicella/chickenpox vaccines for a period of up to three months.

After administration of Berirab 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 four months. 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., anti-A, anti-B and anti-D, may interfere with some serological tests for red cell allo-antibodies (e.g. Coombs` test).

4.6 Fertility, pregnancy and lactation

The safety of Berirab P for use in human pregnancy has not been established in controlled clinical trials. Long lasting clinical experience with immunoglobulins suggests that no harmful effects on the course of pregnancy, on the foetus or the neonate are to be expected.

4.7 Effects on ability to drive and use machines

No effects on the ability to drive and use machines have been observed.

4.8 Adverse reactions

Summary of the safety profile

In rare cases the following adverse reactions may occur:

- Immune system disorders
  Allergic reaction including fall in blood pressure, dyspnoea, cutaneous reaction, in isolated cases reaching as far as anaphylactic shock, even when the patient has shown no hypersensitivity to previous administration of immunoglobulins.
- Cardiac disorders/Vascular disorders
  Cardiovascular reactions particularly if the product is inadvertently injected intravascularly.
- General disorders
  Chills, fever, headache, malaise, nausea, vomiting, arthralgia, moderate back pain.
- Local reactions at the injection site
  Pain, tenderness, swelling.

For safety with respect to transmissible agents, see section 4.4.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions.

4.9 Overdose

Consequences of an overdose are not known. Nevertheless, the dose should never be raised (interference with antibody production related to vaccination, see section 4.2).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: immune sera and immunoglobulins, human rabies immunoglobulin
ATC-code: J06BB05

Mechanism of action

Berirab P is prepared from human plasma. Berirab P contains mainly immunoglobulin G (IgG) with a specifically high concentration of antibodies directed against the rabies virus.[2]
Berirab P administration may raise the relevant antibodies to levels sufficient to reduce the incidence of serious rabies disease in a person who may be exposed to rabies virus.

5.2 Pharmacokinetic properties

Absorption and Distribution

Human rabies immunoglobulin for intramuscular administration is bioavailable in the recipient's circulation after 2 to 3 days.
Human rabies immunoglobulin has a half-life of about 3 to 4 weeks. This half-life may vary from patient to patient.

Elimination

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

5.3 Preclinical data

The active ingredient human rabies immunoglobulin is derived from human plasma and acts like endogenous constituent of plasma.
Single dose intramuscular application of immunoglobulin to various animal species did not reveal toxic effects. Preclinical studies with repeated dose applications (chronic toxicity, carcinogenicity and mutagenicity) cannot be reasonably performed in conventional animal models due to the development of antibodies following the application of heterologous human proteins.

5.4 Clinical studies

[n.a.]

6. PHARMACEUTICAL PARTICULARS

6.1 Incompatibilities

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

6.2 Shelf life

3 years

Stability after first opening:
Berirab P is intended for single-use only. Once the container has been opened the contents have to be used immediately.

6.3 Precautions for storage

Berirab P is to be stored at +2°C to +8°C (refrigerate).

Do not freeze!

Keep the vial in the outer carton in order to protect its content from light.

Keep out of the reach and sight of children!

6.4 Nature and contents of container

Immediate container

SCF syringe of colourless tube glass (type I, Ph. Eur.)

Pack sizes

1 pre-filled syringe of 2 ml

1 pre-filled syringe of 5 ml

6.5 Precautions for use and handling

Berirab P is a sterile, ready-for-use solution and should be brought to room or body temperature before use.[2]

Do not use solutions which are cloudy or contain residues (deposits/particles).

Do not use Berirab P beyond the expiration date on the product label.

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

References

[1] 3.2.P.5.1 Module. Specification for excipients

[2] Core SmPC for Human Rabies Immunoglobulin for Intramuscular Use (CPMP/BPWG/3728/02) 01.Feb.2006. https://www.ema.europa.eu/en/documents/scientific-guideline/core-spc-human-rabies-immunoglobulin-intramuscular-use-cpmp/bpwg/3728/02_en.pdf

[3] WHO Rabies Recommendations 2018: Rabies vaccines and immunoglobulins: WHO position Summary of 2017 updates

[4] Rabies vaccines and immunoglobulins: WHO position April 2018 Rabies vaccines: WHO position paper – April 2018

[5] WHO homepage for rabies management: https://www.who.int/ith/vaccines/rabies/en/

[6] WHO FAQs on Rabies https://www.who.int/docs/default-source/ntds/rabies/rabies-clinicians-faqs-20sep2018.pdf

[7] Ravish S. Haradanhalli, Nidhi Fotedar, Nitu Kumari & D. H. Ashwath Narayana (2022) Safety and clinical efficacy of human rabies immunoglobulin in post exposure prophylaxis for category III animal exposures, Human Vaccines & Immunotherapeutics, DOI: 10.1080/21645515.2022.2081024

HISTORY OF REVISIONS

Version No.	Revision Date	Reason for Change
1.0	02.DEC.2016	New CCDS Template and Periodic Routine Review (Editorial Change), GLRC sign-off.
2.0	25.NOV.2019	Tri-annual update.
3.0	15.SEP.2022	Clarify intralesional as a method of administration / new template format