Proposed Professional Information

SCHEDULING STATUS

S4

1 NAME OF THE MEDICINE

Rhesugam IM, 500 IU (100 micrograms)/2 ml, solution for injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Human anti-D (Rh) immunoglobulin

Each 2 ml ampoule contains 500 IU (100 micrograms) of human anti-D (Rh) immunoglobulin.

*100 micrograms of Human anti-D (Rh) immunoglobulin corresponds to 500 International Units (IU).

One ml contains 250 IU (50 micrograms) Human anti-D (Rh) immunoglobulin.

The potency is determined using the European Pharmacopoeia assay. The equivalence in International Units of the International Reference Preparation is stated by the World Health Organization.

Rhesugam IM contains immunoglobulin derived from pooled human plasma, sourced from healthy Rh-negative donors, with a high titre of antibodies to the D (Rh) erythrocyte antigen.

Each unit of plasma has been individually tested and found non-reactive for hepatitis B surface antigen (HBsAg), antibodies to the hepatitis C virus (HCV) and antibodies to the human immunodeficiency viruses, HIV-1 and HIV-2, using approved methods.

Rhesugam IM is prepared by cold ethanol fractionation, to further reduce the risk of viral transmission.

In addition, only plasma pools tested and found non-reactive for anti-HIV-1 & -2, HBsAg and anti-HCV by serological testing; and for HIV, HCV, hepatitis B virus (HBV) and hepatitis A virus (HAV) by Nucleic Acid Amplification Techniques (NAT), are used in the manufacture of **Rhesugam IM**.

This preparation does not contain any antimicrobial preservatives.

Rhesugam IM is sugar free.

For a full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Solution for injection.

The solution is a colourless, pale yellow to light brown liquid exhibiting a slight opalescence. During storage, it may show formation of slight turbidity or a small amount of particulate matter.

Rhesugam IM has a pH of between 5,0 - 7,2.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

1. Antenatal

Rhesugam IM is indicated for antenatal prophylaxis when a Rh-negative mother is known to be carrying a Rh-positive child or if the Rh-status of the foetus is unknown. It is specifically recommended after the following potentially sensitising events:

- Amniocentesis
- Antepartum haemorrhage
- Abdominal trauma
- External cephalic version
- Ectopic pregnancy
- Chorionic villus sampling
- Stillbirth
- Foetal Blood Sampling

2. Abortions

Rhesugam IM should be given to all Rh-negative women after:

- Therapeutic abortions.
- Spontaneous abortions, after 12 weeks gestation, and especially if there is surgical intervention.
- Early spontaneous abortions (first trimester). Sensitisation can occur as early as eight weeks gestation.
- Threatened abortions after 12 weeks gestation.
- Induced abortions (termination of pregnancy)

3. Postnatal

Rhesugam IM is essential after **every** delivery involving a Rh-negative mother and a Rh-positive child, provided that there is no evidence of prior maternal sensitisation to the D (Rh) erythrocyte antigen. If the Rh type of the neonate cannot be determined, this preparation should still be administered to the mother.

If antepartum anti-D (Rh) immunoglobulin has been given, an additional postpartum dose is also necessary. Rh-negative women with blood group antibodies other than anti-D should still be treated with this preparation.

4. Rhesus Incompatible Transfusions

Although the transfusion of Rh-negative individuals with Rh-positive red cell concentrate, whole blood and platelets should be avoided whenever possible; anti-D (Rh) immunoglobulin may also be given in this instance. It is particularly important after transfusion of a Rh-negative woman of child-bearing age with Rh-positive red blood cells, whole blood or platelets.

4.2 Posology and method of administration

Posology

For optimal protection, anti-D (Rh) immunoglobulin should be administered intramuscularly as soon as possible, but always within 72 hours of the possible sensitising event.

Immunisation to the D (Rh) erythrocyte antigen is directly related to the volume of Rh-positive cells infused or to the site of a foeto-maternal haemorrhage. A 500 IU dose gives protection for foeto-maternal haemorrhage of up to 4 ml of red cells. Post-delivery or following a potentially sensitising event after 20 weeks gestation, a **Kleihauer-Betke** test (which determines the number of foetal cells in the mother's circulation) which should be done at the time when the dose of anti-D is being considered. If this shows that the foeto-maternal bleed is larger than 4 ml, an additional dose of anti-D (Rh) immunoglobulin must be given. This is calculated using the formula that 125 IU of anti-D (Rh) immunoglobulin is administered per 1 ml of red cells.

Recommended dosages

The following are recommended dosages of **Rhesugam IM**. Please note that where appropriate, dosages should be determined by doing a **Kleihauer-Betke test** immediately after any sensitising event.

Indication	Recommended Dosage
Pregnancy associated indications:	
Antenatal prophylaxis	500 IU (100 µg) is given at 28 and/or 34 weeks gestation. If the infant is Rh-positive, a similar or higher dose should be administered after delivery.
Prophylaxis following potentially sensitising events, including abortions	250 IU (50 µg) is recommended for events up to 20 weeks. For events occurring after 20 weeks, a dose of 500 IU (100 µg) is recommended.
Postnatal prophylaxis	500 IU (100 µg) is recommended.
Non-pregnancy associated indications	
Transfusion of Rh-incompatible blood	The dose is calculated to clear the estimated quantity of red cells given, i.e. 125 IU (25 µg) for each 1 ml of red cells.
Transfusion of Rh-positive platelets in Rh-negative women of childbearing age	250 IU (50 µg) for each dose of platelets (i.e. 5-6 units), if more than 10 units are used, administer 500 IU (100 ug).

Method of administration

Intramuscular route.

If anti-D (Rh) immunoglobulin is introduced into fat rather than into muscle, the uptake could be substantially lowered. Anti-D (Rh) immunoglobulin should therefore be injected into the deltoid muscle.

If a large volume (> 5 ml) is required, it is recommended that this be administered in divided doses at different sites.

For instructions on handling and disposal of this injection, see section 6.6.

4.3 Contraindications

- Hypersensitivity to the active substance (human anti-D (Rh) immunoglobulin) or to any of the excipients listed in section 6.1.
- Hypersensitivity to human immunoglobulins.

4.4 Special warnings and precautions for use

Ensure that Rhesugam IM is not administered into a blood vessel because of the risk of shock.

Anti-D (Rh) immunoglobulin is not effective once the mother has formed anti-D (Rh) antibodies.

Rhesugam IM should not be given to:

- The baby
- The Rh-positive mother
- A Rh-negative mother who has given birth to a known to a known Rh-negative baby
- A Rh-negative mother with previous sensitisation to the D (Rh) erythrocyte antigen.

Treating Rh-negative individuals with anti-D (Rh) immunoglobulin poses few risks.

It should be noted that inadequate therapy will result in Rh allo-immunisation.

Intramuscular injections are not advocated for persons with bleeding disorders, unless special precautions are taken.

Hypersensitivity

True hypersensitivity reactions are rare.

Anaphylactic reactions may occur especially if this intramuscular preparation is given intravenously. Measures to treat anaphylaxis, including adrenaline, must be immediately available when administering **Rhesugam IM.**

Persons with selective immunoglobulin A (IgA) deficiency may develop antibodies to the small amount of IgA in this preparation, leading to sensitisation and subsequent reaction to IgA-containing material. The risk-benefit ratio in patients with a history of IgA deficiency or severe anaphylactic reactions to plasma products should be considered.

Haemolytic reactions

Patients in receipt of incompatible transfusion, who receive very large doses of anti-D (Rh) immunoglobulin, should be monitored clinically and by biological parameters, because of the risk of haemolytic reaction.

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 pathogens. Consideration should be given to appropriate vaccination of patients receiving human blood or plasma-derived medicines on a routine basis.

The measures taken are considered effective for enveloped viruses such as HIV, HBV and HCV. The measures taken may be of limited value against non-enveloped viruses such as 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 viral safety.

Traceability

It is strongly recommended that when **Rhesugam IM** 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 Interaction with other medicines and other forms of interactions

Live attenuated virus vaccines

Active immunisation with live virus vaccines (e.g. measles, mumps or rubella) should be postponed for 3 months after the last administration of anti-D (Rh) immunoglobulin, as the efficacy of the live virus vaccine may be impaired.

If anti-D (Rh) immunoglobulin needs to be administered within 2 -4 weeks of a live virus vaccination, then the efficacy of such a vaccination may be impaired.

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.

4.6 Fertility, pregnancy and lactation

Pregnancy and breastfeeding

This medicine has been used in pregnancy. No harmful effects are known with respect to the course of pregnancy and to the newborn and neonate.

Fertility

No data are available.

4.7 Effects on ability to drive and use machines

Rhesugam IM may cause dizziness and other side effects. 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, allergic reactions, nausea, low blood pressure, back pain and local reactions may occur occasionally.

List of adverse reactions

MedDRA Standard System Organ Class	**Undesirable effects**	**Frequency**
Immune system disorders	Hypersensitivity	Unknown
	Anaphylactic reaction	Unknown
Nervous system disorders	Headache	Unknown
	Dizziness	Unknown
Cardiac disorders	Tachycardia	Unknown
Vascular disorders	Hypotension	Unknown
	Shock	Unknown
	Flushing	Unknown
Gastrointestinal disorders	Nausea	Unknown
	Vomiting	Unknown
Skin & subcutaneous tissue disorders	Skin reactions	Unknown
Musculoskeletal and connective tissue disorder	Back pain	Unknown
General disorders and administration site conditions	Chills	Unknown
	Pyrexia	Unknown
	Injection site pain Administration site reaction	Unknown

Transmissible agents

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

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. Health care providers are requested to report any suspected adverse reactions to SAHPRA via the Med safety APP (Medsafety X SAHPRA) and eReporting platform (https://primaryreporting.who-umc.org/ZA) found on SAHPRA website or to National Bioproducts Institute via the email address Pharmacovigilance@nbisa.org.za.

4.9 Overdose

Consequences of an overdose are not known.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: immune sera and immunoglobulins: anti-D (Rh) immunoglobulin, ATC code: J06BB01

Category and class: A. 30.1 Biologicals (Antibodies).

Anti-D (Rh) immunoglobulin prevents active immunisation to the D (Rh) erythrocyte antigen in Rh-negative individuals exposed to Rh-positive blood.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Glycine

Sodium chloride

Sodium hydroxide (for pH-adjustment)

Hydrochloric acid (for pH-adjustment)

Human albumin

Human hepatitis B immunoglobulin

Human normal immunoglobulin

Water for injections

6.2 Incompatibilities

In the absence of compatibility studies, this medicine must not be mixed with other medicines.

6.3 Shelf life

3 years.

From a microbiological point of view, the product should be used immediately after opening. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user.

6.4 Special precautions for storage

Transport within 72 hours below 37 °C.

Store in a refrigerator between 2 °C and 8 °C.

Keep the ampoule in the outer carton until required for use.

Do not freeze.

Protect from light.

For in-use storage conditions, see section 6.3.

6.5 Nature and contents of container

Rhesugam IM is presented as a single dose, and packaged in a 2 ml clear and colourless, type I glass ampoule marked with a red ring.

6.6 Special precautions for disposal and other handling

Warm the ampoule to body temperature before injecting intramuscularly.

The solution is a clear, slightly opalescent liquid, which is almost colourless or pale-yellow to light brown.

During storage, it may show formation of slight turbidity or a small amount of particulate matter.

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

7 HOLDER OF CERTIFICATE OF REGISTRATION

NATIONAL BIOPRODUCTS INSTITUTE NPC

Company Reg. No. 1994/002044/08

NPO Reg. No. 020-898-NPO

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8 REGISTRATION NUMBERS

T/30.2/750

Namibia	S2
Reg. No.:	04/30.2/1141

9 DATE OF FIRST AUTHORISATION / RENEWAL OF AUTHORISATION

Registration date: 26 September 1995

10 DATE OF REVISION OF THE TEXT