European Medicines Agency
Human Medicines Evaluation Unit

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COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE (CHMP)

GUIDELINE ON THE CORE SPC FOR HUMAN ANTI-D IMMUNOGLOBULIN FOR INTRAVENOUS USE - Revision 1

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This guideline replaces the guidance on human anti-D immunoglobulin for intravenous use in the Core SPC For Human Anti-D Immunoglobulin for Intravenous and/or Intramuscular Use, reference CPMP/BPWG/574/99 dated 29 June 2000

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CORE SPC
FOR
HUMAN ANTI-D IMMUNOGLOBULIN FOR INTRAVENOUS USE

Where a product is suitable for intravenous use but also has recommendations for intramuscular use in its SPC, the Guideline on the Core SPC For Human Anti-D Immunoglobulin For Intramuscular Use (CPMP/BPWG/574/99 Rev 1) should be taken into account.

The QRD Product Information template with explanatory notes and the convention to be followed for QRD templates** provide general guidance on format and text and should be read in conjunction with the core SPC and the Guideline on Summary of Product Characteristics.*
*In addition, for the content of sections 4.4 and 4.8 concerning transmissible agents, refer to the current version of the "Note for Guidance on the Warning on Transmissible Agents in SPCs and Package Leaflets for plasma-derived medicinal products" (CPMP/BPWG/BWP/561/03).****

This core SPC covers human anti-D immunoglobulin for intravenous administration defined by the European Pharmacopoeia monograph 1527.

* *http://www.emea.eu.int/htms/human/qrd/qrdplt/AnnotatedTemplate-H.pdf*
** *http://www.emea.eu.int/htms/human/qrd/qrdplt/qrdconvention.pdf*
*** *http://www.emea.eu.int/pdfs/human/bpwg/056103en.pdf*

1. NAME OF THE MEDICINAL PRODUCT

{(Invented) name, strength, pharmaceutical form}

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Human anti-D immunoglobulin

[Product specific information on quantitative composition. Include: human protein content and minimum content of IgG (e.g. human protein x g/l of which at least y% is IgG), content of specific immunoglobulin IU/ml and per container, maximum IgA content.]*

*100 micrograms of human anti-D immunoglobulin correspond to 500 international units (IU).

For excipients, see section 6.1

3. PHARMACEUTICAL FORM

[Product specific]

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Prevention of Rh (D) immunisation in Rh(D) negative women

- **Antenatal prophylaxis**
  - ▹ Planned antenatal prophylaxis
  - ▹ Antenatal prophylaxis following complications of pregnancy including:

    Abortion/threatened abortion, ectopic pregnancy or hydatidiform mole, intrauterine fetal death (IUFD), transplacental haemorrhage (TPH) resulting from ante-partum haemorrhage (APH), amniocentesis, chorionic biopsy, obstetric manipulative procedures e.g. external version, invasive interventions, cordocentesis, blunt abdominal trauma or fetal therapeutic intervention
- **Postnatal prophylaxis**
  - ▹ Pregnancy/delivery of a Rh(D) positive (D, D^{weak}, $D^{partial}$) baby

Treatment of Rh(D) negative persons after incompatible transfusions of Rh(D) positive blood or other products containing red blood cells e.g. platelet concentrate.

<Consideration should also be given to other official guidance on the appropriate use of human anti-D immunoglobulin for intravenous use.>

[Other product specific indications]

4.2 Posology and method of administration

Posology

[Product specific. Posology recommendations differ in the EU Member States. The dose ranges given in section 4.2 below reflect the range of dosage used in clinical practice within the EU. If the doses administered in the clinical trials are within these ranges, then these ranges are to be adopted for the product specific SPC. If a product is only for authorisation in countries with the same posology recommendations, then the country-specific posology recommendations may be included in the product specific SPC instead of these ranges. The doses used in the clinical trials are to be mentioned in section 5.1.]

The dose of anti-D immunoglobulin should be determined according to the level of exposure to Rh(D) positive red blood cells and based on the knowledge that 0.5 ml of packed Rh(D) positive red blood cells or 1 ml of Rh (D) positive blood is neutralised by approximately 10 micrograms (50 IU) of anti-D immunoglobulin.

The following doses are recommended based on the clinical studies performed with {(Invented) name of product}.

<Consideration should also be given to dose and dose schedules for human anti-D immunoglobulin for intravenous use recommended in other official guidance.>

Prevention of Rh (D) immunisation in Rh(D) negative women

- **Antenatal prophylaxis** According to general recommendations, currently administered doses range from 50 – 330 micrograms or 250 - 1650 IU. For specific study details see Section 5.1.
  - ▹ Planned antenatal prophylaxis:

    A single dose at 28 - 30 weeks of gestation or two doses at 28 and 34 weeks.
  - ▹ Antenatal prophylaxis following complications of pregnancy:

    A single dose should be administered as soon as possible and within 72 hours and if necessary repeated at 6 – 12 week intervals throughout the pregnancy.
- **Postpartum prophylaxis** According to general recommendations, currently administered doses range from 100 – 300 micrograms or 500 – 1500 IU. For specific study details see Section 5.1. If the lower dose (100 micrograms or 500 IU) is administered then testing of the amount of fetal maternal haemorrhage should be performed.

  For postnatal use, the product should be administered as soon as possible within 72 hours of delivery of an Rh positive (D, D^{weak}, $D^{partial}$) infant. If more than 72 hours have elapsed, the product should not be withheld but administered as soon as possible.

  The post partum dose must still be given even when antepartum prophylaxis has been administered and even if residual activity from antenatal prophylaxis can be demonstrated in maternal serum.

If a large feto-maternal haemorrhage (> 4 ml (0.7%-0. 8% of women)) is suspected, e.g. in the event of fetal/neonatal anaemia or intrauterine fetal death, its extent should be determined by a suitable method e.g. Kleihauer-Betke acid elution test to detect fetal HbF or flow cytometry which specifically identifies Rh D positive cells. Additional doses of anti-D immunoglobulin should be administered accordingly (10 micrograms or 50 IU) per 0.5 ml fetal red blood cells).

Incompatible transfusions of red blood cells (RBCs)

The recommended dose is 20 micrograms (100 IU) anti-D immunoglobulin per 2ml of transfused Rh (D) positive blood or per 1 ml of RBC concentrate. The appropriate dose should be determined in consultation with a specialist in blood transfusion. Follow-up tests for Rh D positive RBCs should be done every 48 hours and further anti-D administered until all Rh D positive RBCs have cleared from the circulation. A maximum dose of 3000 micrograms (15000 IU) is sufficient in the case of larger incompatible transfusions independent of whether the transfusion volume is greater than 300 ml of Rh (D) positive red blood cells.

[Product specific for intravenous products that also have dosage recommendation for intramuscular use:] <Intravenous use is recommended as it will achieve adequate plasma levels immediately.>

Method of administration

For intravenous use administered by slow injection.

4.3 Contraindications

Hypersensitivity to any of the components.

Hypersensitivity to human immunoglobulins.

4.4 Special warnings and special precautions for use

In the case of postpartum use, the product is intended for maternal administration. It should not be given to the new-born infant.

The product is neither intended for use in Rh(D) positive women nor for women already immunised to Rh(D) antigen.

True hypersensitivity reactions are rare but allergic type responses to anti-D immunoglobulin may occur.

[*Product specific*]
<{(Invented) name of the product} contains a small quantity of IgA. Although anti-D immunoglobulin has been used successfully to treat selected IgA deficient individuals, 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. The physician must therefore weigh the benefit of treatment with {(invented) name of product} against the potential risks of hypersensitivity reactions.>

Rarely, human anti-D immunoglobulin can induce a fall in blood pressure with anaphylactic reaction, even in patients who have tolerated previous treatment with human immunoglobulin.

Suspicion of allergic or anaphylactic type reactions requires immediate discontinuation of the injection. In case of shock, standard medical treatment for shock should be implemented.

[The text to be inserted here for transmissible agents should be in accordance with the current version of the guideline on the Warning on Transmissible Agents in SPCs and Package Leaflets for plasma-derived medicinal products (CPMP/BPWG/BWP/561/03]

4.5 Interactions with other medicinal products 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 immunoglobulin, as the efficacy of the live virus vaccine may be impaired.

If anti-D 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.

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 antiglobulin test (Coombs' test) particularly in Rh(D) positive neonates whose mothers have received antepartum prophylaxis.

4.6 Pregnancy and lactation

This medicinal product is intended for use in pregnancy.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

<There are no robust data on the frequency of undesirable effects from clinical trials. The following undesirable effects have been reported: >

<The following undesirable effects have been reported <from {x} patients in clinical studies> <and from post-marketing experience>: >

[If there are robust data on the frequency of undesirable effects from clinical trials the section should be prepared in line with the general provisions of the SPC guideline.]

MedDRA Standard System Organ Class	Undesirable effects	<Frequency>
Immune system disorders	Hypersensitivity, anaphylactic shock	
Nervous system disorders	Headache	
Cardiac disorders	Tachycardia	
Vascular disorders	Hypotension	
Gastrointestinal disorders	Nausea, vomiting	
Skin and subcutaneous tissue disorders	Skin reaction, erythema, itching, pruritus	
Musculoskeletal and connective tissue disorders	Arthralgia	
General disorders and administration site conditions	Fever, malaise, chill	

[The text to be inserted here for transmissible agents should be in accordance with the current version of the guideline on the Warning on Transmissible Agents in SPCs and Package Leaflets for plasma-derived medicinal products (CPMP/BPWG/BWP/561/03]

4.9 Overdose

Consequences of an overdose are not known. Patients in receipt of incompatible transfusion, who receive very large doses of anti-D immunoglobulin, should be monitored clinically and by biological parameters, because of the risk of haemolytic reaction.

In other Rh(D) negative individuals overdosage should not lead to more frequent or more severe undesirable effects than the normal dose.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: immune sera and immunoglobulins

- anti-D (Rh) immunoglobulin ATC code: J06BB01.

Anti-D immunoglobulin contains specific antibodies (IgG) against the D (Rh) antigen of human erythrocytes.

[Product specific] It can also contain antibodies to other Rh antigens e.g. anti-Rh C antibodies.

During pregnancy, and especially at the time of childbirth, fetal red blood cells may enter the maternal circulation. When the woman is Rh(D)-negative and the fetus Rh(D)-positive, the woman may become immunised to the Rh(D) antigen and produce anti-Rh(D) antibodies which cross the placenta and may cause haemolytic disease of the newborn. Passive immunisation with anti-D immunoglobulin prevents Rh(D) immunisation in more than 99% of cases provided that a sufficient dose of anti-D immunoglobulin is administered soon enough after exposure to Rh(D)-positive fetal red blood cells.

The mechanism by which anti-D immunoglobulin suppresses immunisation to Rh(D)-positive red cells is not known. Suppression may be related to the clearance of the red cells from the circulation before they reach immunocompetent sites or, it may be due to more complex mechanisms involving recognition of foreign antigen and antigen presentation by the appropriate cells at the appropriate sites in the presence or absence of antibody.

[A summary of the results from clinical trials, including the posology investigated, should be included here.]

5.2 Pharmacokinetic properties

The bioavailability of human anti-D immunoglobulin for intravenous use is complete and immediate. IgG is quickly distributed between plasma and extravascular fluid.

[Product specific:]

Human anti-D immunoglobulin has a half-life of about 3-4 weeks. This half-life may vary from patient to patient.

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

5.3 Preclinical safety data

[Product specific]

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

[Product specific. Where applicable, the amount of albumin added as a stabiliser should be stated (Ph. Eur. labelling requirement).]

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products.

[Product specific]

6.3 Shelf-life

[Product specific]

6.4 Special precautions for storage

[Product specific]

6.5 Nature and contents of container

[Product specific]

6.6 Instructions for use and handling and disposal

[Product specific]

The product should be brought to room or body temperature before use.

<Total reconstitution should be obtained within *[product specific time]*.>

The solution should be clear or slightly opalescent. Do not use solutions that are cloudy or have deposits. <Reconstituted products should be inspected visually for particulate matter and discoloration prior to administration.>

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

7. MARKETING AUTHORISATION HOLDER

{Name and address}

8. MARKETING AUTHORISATION NUMBER(S)

[Product specific]

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

[Product specific]

10. DATE OF REVISION OF THE TEXT

[Product specific]