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Committee for medicinal products for human use (CHMP)

Guideline on the core SmPC for human Anti-D immunoglobulin for intramuscular use

Draft

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This revised guideline replaces 'Guideline on the core SPC for human anti-D immunoglobulin for Intramuscular Use' (CPMP/BPWP/574/99 Rev. 1) dated 20 September 2007.

Comments should be provided using this template. The completed comments form should be sent to BPWPSecretariat@ema.europa.eu.

Keywords	***Anti-D immunoglobulin, pregnancy, incompatible transfusion, Rh(D) negative, SPC***

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Executive summary

This guideline describes the information to be included in the Summary of Product Characteristics (SmPC) for a human anti-D immunoglobulin for intramuscular use.

With respect to the previous version, this Core SmPC has been adapted to the current QRD template. The method of administration for overweight patients has been specified.

Furthermore, although thromboembolic events have not been observed with products intended for intramuscular use, new special warnings have been added regarding the potential risk of thromboembolism, and about the need of an adequate hydration, in particular in patients with risk factors and/or treated with higher doses.

With respect to the i.v.anti D Ig, this Core SmPC is specific for anti D Ig intended for intramuscular use.

Timeline history of core SmPC: The original core SPC was published by the European Commission in 1992. This was superseded by the core SPC for Human Anti-D Immunoglobulin for Intravenous and/or Intramuscular Use, reference CPMP/BPWG/574/99 dated 29 June 2000 and which came into effect on 1 December 2000. Revision 1, dated 20 September 2007, came into effect on 1 April 2008. Revision 2 of the core SmPC introduces a warning on thromboembolism in 4.4 and includes a text relating to procoagulant activity in the introduction. A general update of the core SmPC has been undertaken.

1. Introduction (background)

The purpose of this core SmPC is to provide applicants and regulators with harmonised guidance on the information to be included in the Summary of Product Characteristics (SmPC) for a human anti-D immunoglobulin for intramuscular use, which is indicated for use in prevention of Rh(D) immunisation in antenatal and postnatal prophylaxis, and treatment of Rh(D) negative persons after incompatible transfusions containing Rh(D) positive red blood cells.

This core SmPC should be read in conjunction with the QRD product template with explanatory notes ('QRD annotated template')[1] and the convention to be followed for QRD templates[2] which provide general guidance on format and text for SmPC, labelling and package leaflet, and with the Guideline on summary of product characteristics[3] which provides general principles of presenting information on medicinal products. It is very useful to provide information for healthcare professionals on posology and method of administration at the end of the package leaflet since the SmPC is not always readily available. See the QRD annotated template for further guidance on how to present such information.

To date human anti-D immunoglobulin for intramuscular use has not been associated with risks of TEE (thromboembolic events), thus MAHs have not been required to investigate and remove potential procoagulant agents. However these products can be administered to patients with high risk of thrombosis. Therefore, in order to proactively prevent any potential risks in this specific population, manufacturers are encouraged to investigate potential procoagulant activity in their product and if present consider whether levels could be reduced.

[1] http://www.ema.europa.eu/docs/en_GB/document_library/Template_or_form/2009/10/WC500004368.pdf
[2] http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2009/10/WC500005091.pdf
[3] http://ec.europa.eu/health/files/eudralex/vol-2/c/smpc_guideline_rev2_en.pdf

2. Scope

This core SmPC covers human anti-D immunoglobulin for intramuscular administration defined by the European Pharmacopoeia monograph 557.

3. Legal basis and relevant guidelines

This guideline has to be read in conjunction with Article 11 of Directive 2001/83 as amended, and the introduction and general principles (4) and part I of the Annex I to Directive 2001/83 as amended.

Relevant guidelines to refer to are:

- Core SmPC for human normal immunoglobulin for subcutaneous and intramuscular use (CPMP/BPWG/143744/2011 Rev. 1)

- CMDh annotated QRD template for MRP/DCP (Version 9.1, 06/2015)

In addition, for the content of sections 4.4 and 4.8 concerning transmissible agents, refer to the current version of the Guideline on the warning on transmissible agents in SmPCs and package leaflets for plasma-derived medicinal products (EMA/CHMP/BWP/360642/2010 rev. 1)[4].

[4] http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2011/12/WC500119001.pdf

1. NAME OF THE MEDICINAL PRODUCT

{(Invented) name strength pharmaceutical form}

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

[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.]*

Human protein content {x} g/l of which at least {y} % is IgG.

Each {container} contains {x*} IU *[as per labelled content]* human Anti-D immunoglobulin.

One ml contains {y} IU human Anti-D immunoglobulin <after reconstitution>.

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

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.

Distribution of the IgG subclasses (approx. values):
IgG1 ..... {XX.X}%
IgG2 ..... {XX.X}%
IgG3 ..... {XX.X}%
IgG4 ..... {XX.X}%

The maximum IgA content is {x} micrograms/ml.

Produced from the plasma of human donors.

[Product specific information on excipients]

3. PHARMACEUTICAL FORM

[Product specific]

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Prevention of Rh (D) immunisation in Rh(D) negative childbearing age 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
  - ▹ Delivery of a Rh(D) positive (D, D^{weak}, $D^{partial}$) baby

Treatment of Rh(D) negative childbearing age women 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 intramuscular 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 SmPC. 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 SmPC 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.

<Consideration should also be given to dose and dose schedules for human anti-D immunoglobulin for intravenous use recommended in other official or Member States 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*Planned antenatal proph*ylaxis:

  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.

- *Postnatal 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 to the mother 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 postnatal dose must still be given even when antenatal 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. It is recommended the consultation with a specialist in transfusion medicine in order to evaluate the feasibility of a red cell exchange procedure to reduce the load of D positive red cells in circulation and to define dose of anti-D immunoglobulin required to suppress immunisation. Follow-up tests for D positive red cells should be undertaken every 48 hours and further anti-D given until there are no detectable D positive red cells in circulation. In any case, due to possible risk of haemolysis it is suggested to not exceed a maximum dose of 3000 micrograms (15000 IU).

The use of an alternative intravenous product is recommended as it will achieve adequate plasma levels immediately. If no intravenous product is available, the very large volume should be administered intramuscularly over a period of several days (see section 4.4).

Paediatric population
[Product Specific]

Method of administration

Intramuscular use.

If a large volume (>2 ml for children or >5 ml for adults) is required, it is recommended to administer this in divided doses at different sites.

If intramuscular administration is contraindicated (bleeding disorders), an alternative intravenous product should be used.

Overweight patients

In case of overweight/obese patients the use of an intravenous anti-D product should be considered (see section 4.4).

4.3 Contraindications

<Hypersensitivity to the active substance(s) or to any of the excipients listed in section 6.1 <or {name of the residue(s)}>.>(.

Hypersensitivity to human immunoglobulins <, especially in patients with antibodies against IgA>.

{(Invented) name} must not be given for intravascular use.

It must also not be administered for intramuscular use in case of severe thrombocytopenia and in other disorders of haemostasis.

Patients who are Rh (D) positive

Patients already immunized against the antigen D.

4.4 Special warnings and precautions for use

Ensure that {(invented) name } is not administered into a blood vessel, because of the risk of shock.

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

Hypersensitivity

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 plasma derived medicinal products 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.

Haemolytic reactions

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.

Thromboembolism

Arterial and venous thromboembolic events including myocardial infarction, stroke, deep venous thrombosis and pulmonary embolism have been associated with the use of immunoglobulins. Although thromboembolic events have not been observed for {(invented) name of product} 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), especially when higher doses of [Invented name of the product] are prescribed. If high doses are required see last paragraph of posology in section 4.2.
Patients should be informed about first symptoms of thromboembolic events including 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.

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 antenatal prophylaxis.

Overweight/obese patients

In overweight/obese patients, due to the possible lack of efficacy in case of intramuscular administration, an intravenous anti-D product is recommended.

[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 (EMA/CHMP/BWP/360642/2010 rev. 1).]

4.5 Interaction with other medicinal products and other forms of interaction

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.

4.6 Fertility, pregnancy and lactation

<Pregnancy>This medicinal product is intended for use in pregnancy.

<Breast-feeding>

This medicinal product can be used during breastfeeding.

<Immunoglobulins are excreted in human milk. No study drug-related adverse events were reported in children delivered of <___> women who received postpartum administration of {Invented name}>,

<Fertility>

<No> animal fertility studies have been conducted <with {Invented name}>., Clinical experience with human anti-D immunoglobulin suggests that no harmful effects on fertility are to be expected.

4.7 Effects on ability to drive and use machines

{(Invented) name} has no influence on the ability to drive and use machines

4.8 Undesirable effects

Summary of the safety profile

Adverse reactions such as chills, headache, dizziness, fever, vomiting, allergic reactions, nausea, arthralgia, low blood pressure and moderate low back pain may occur occasionally.
Rarely human immunoglobulins may cause a sudden fall in blood pressure and, in isolated cases, anaphylactic shock, even when the patient has shown no hypersensitivity to previous administration.
Local reactions at infusion sites: swelling, soreness, redness, induration, local heat, itching, bruising and rash.

The following adverse reactions have been reported <from {x} patients in clinical studies> <and from 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).
<Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.>

MedDRASystem Organ Class	**Adverse reaction**	**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 At the injection site: swelling, pain, erythema, induration, warmth, pruritus, rash, itching	

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. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

<Consequences of an overdose are not known.>

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: immune sera and immunoglobulins, immunoglobulins, specific 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

Human anti-D immunoglobulin for intramuscular administration is slowly absorbed into the recipient's circulation and reaches a maximum after a delay of 2-3 days.

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 cells of the reticuloendothelial system.

5.3 Preclinical safety data

[Product specific]

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

[Product specific]

6.2 Incompatibilities

<In the absence of compatibility studies, 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 Special precautions for disposal <and other handling>

[Product specific]

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

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

The colour can vary from colourless to pale-yellow up to light brown. 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

[Product specific]

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]