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SCIENCE MEDICINES HEALTH

EMA Regulatory requirements for authorisation of anti-D medicines in European countries

EDQM Anti D Working Group- Webinar 2: Production of plasma derived Anti D IgG
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Anti-D immunoglobulins

Products are nationally authorised:

- D-Gam (BPL)
- Gamma Anty-D (Rhogam Ultra-Filtered Plus (Kedrion S.P.A.))
- Biomed-Lublin Wsisz S.A.
- Ig Vena (Kedrion S.P.A.)
- Igamad (Instituto Grifols, S.A.)
- Immunorho
- Rhesonativ (Octapharma)
- Rhogam Ultra-Filtered (Kedrion S.P.A.)
- Rhophylac (Csl Behring Gmbh)
- Хипеpро S/D (Chimimport Pharma Jsc)

Source: Article 57 database

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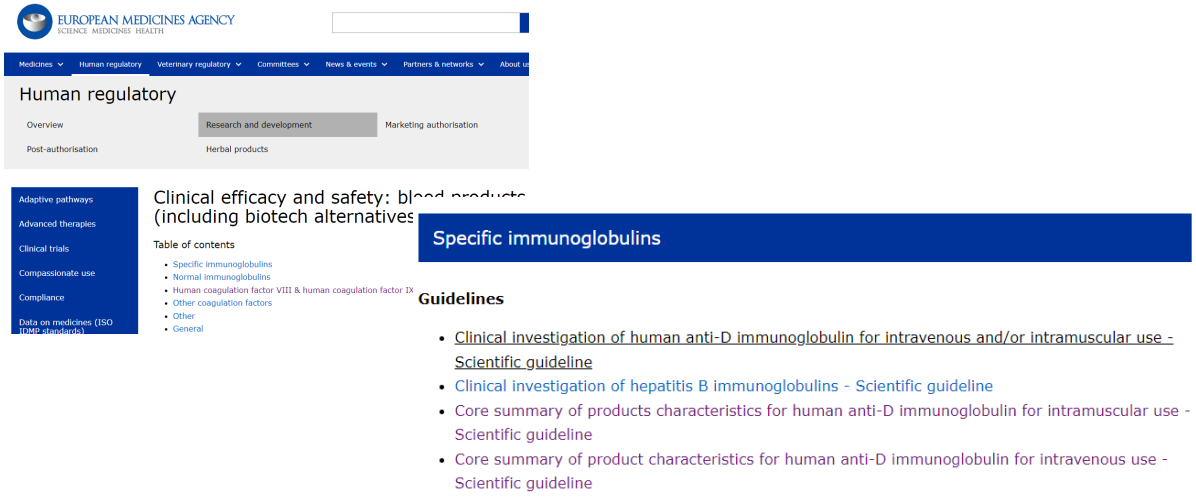
Specific immunoglobulins – anti-D immunoglobulins



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Authorised 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.

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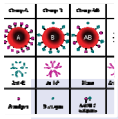
Therapeutic context



Context

- Rhesus disease (Rh (D)) is a condition where antibodies in a pregnant woman's blood destroy her baby's blood cells.
- Problems can develop if the baby's red blood cells cross to the Rh negative mother. This usually happens at delivery when the placenta detaches.
- Rhesus disease doesn't harm the mother, but it can cause the baby to become anaemic and develop newborn jaundice.

Use of Rh (D)

- Accepted that Rh(D) immunisation can be prevented in most cases by giving a dose of anti-D immunoglobulin (anti-D Ig) to Rh(D) negative mothers after delivery of a Rh(D) positive infant, after stillbirth or abortion or any other potentially sensitising event during pregnancy.

WHO

- Recommendations from WHO working groups in 1967 and 1970 were adopted in several countries where haemolytic disease of the new-born caused by anti-D antibodies was a significant cause of perinatal mortality and morbidity.

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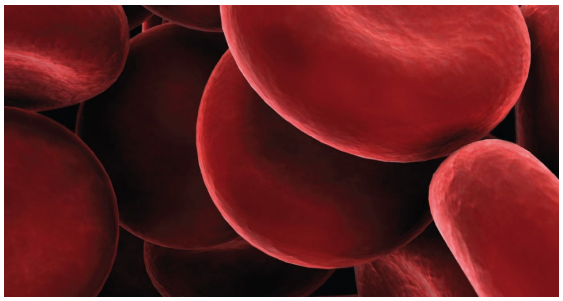
Mechanism of action



- 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.

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Anti-D immunoglobulins

- •Sterile liquid or freeze-dried preparations containing as active substances immunoglobulins, mainly IgG, with specific antibodies against erythrocyte D-antigen.
- •Intended for IM or IV administration. IV need tests and limits for anti-complementary activity and for anti-A and anti-B haemagglutinins.
- •The dosage is determined according to the level of exposure to Rh(D) positive blood, established based on the knowledge that 0.5 ml of packed D positive red cells or 1ml of Rh(D) positive blood is neutralised by approximately 50 IU (10 µg) anti-D immunoglobulin.
- •Indications, dosage and methods of administration differ because of divergent clinical practice in individual Member States.

Manufacturing – specific requirements

Pooled plasma

- Obtained from pooled plasma of donors with sufficient titres of anti-D antibodies.

Viral screening

- Includes validated purification and virus inactivation / removal steps (CHMP recommendations on viral safety)
- Verified by information in Module 3

Non-enveloped virus

- Limited for Hepatitis A virus and parvovirus B19.

Storage

- A pre-treatment serum sample from each patient included in the clinical trials should be stored at -70°C for possible future testing.

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Biological, pharmacodynamic and pharmacokinetic data

- *In vitro* potency assays addressing red cell destruction to assess product comparability
  - Antibody content against different Rh(D) erythrocytes
  - *In vivo* and/or *in vitro* quantification of anti-D antibodies
  - IgG subclasses, in particular IgG1 and IgG3
- The pharmacodynamic effect is established by the biological data for the product and the clinical efficacy studies.
- Single dose pharmacokinetics studies should be carried out in 15 Rh(D) negative subjects, after intravenous and/or intramuscular administration (depending on the desired method of administration).
- Serum clearance, volume of distribution, area under the curve, mean serum half-life (α and β) should be measured.

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Clinical trials

- Cannot be examined using classical principles of clinical trials.
- Surrogate markers should be measured using appropriate methods and time intervals:
  - Absence of anti-D antibodies in the serum of Rh(D) negative women 3-6 months after the delivery of the Rh(D) positive baby.
- 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.
- 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.

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Clinical trials

- Clinical data should be provided to demonstrate the effective prevention of Rh(D) isoimmunization in Rh(D) negative women who are pregnant with a Rh(D) positive fetus (including D, Dweak, Dpartial).
- The study should investigate at least 200 non-immunised patients and should include both ante-partum and post-partum administration.
- Accepted dosage regimen via the desired route of administration.
- Blood samples should be collected just before treatment and at 72 hours and 3-6 months after treatment with the anti-D immunoglobulin.
- The incidence of anti-D antibodies at 3 and 6 months after treatment should be reported.

Thank you for your attention

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Thanks: HAEMWP experts and Ole Weis Bjerrum

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