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**COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE
(CHMP)**

**GUIDELINE ON THE CLINICAL INVESTIGATION OF HUMAN ANTI-D
IMMUNOGLOBULIN
FOR INTRAVENOUS AND/OR INTRAMUSCULAR USE**

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CLINICAL INVESTIGATION OF HUMAN ANTI-D IMMUNOGLOBULIN FOR INTRAVENOUS AND/OR INTRAMUSCULAR USE

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EXECUTIVE SUMMARY

This guideline describes the information to be documented when an application for a marketing authorisation for a human anti-D immunoglobulin is made 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. The guidance covers biological data, clinical trials and patient follow up. Quality aspects are outside the scope of this guideline. Guidance is also provided for authorised products where a significant change in the manufacturing process has been made.

1. INTRODUCTION (background)

The purpose of this guidance is to provide applicants and regulators with harmonised guidance for applications for marketing authorisation for human anti-D immunoglobulin 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.

2. SCOPE

The guidance covers biological data, clinical trials and patient follow up. Quality aspects are outside the scope of this guideline.

3. LEGAL BASIS

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

4. MAIN GUIDELINE TEXT

4.1. INTRODUCTION

Human anti-D immunoglobulin medicinal products are sterile liquid or freeze-dried preparations containing as active substances immunoglobulins, mainly IgG, with specific antibodies against erythrocyte D-antigen. Small quantities of antibodies to other blood group antigens may also be present.

Products may be intended for:

- intramuscular administration (and therefore comply with the Ph. Eur. monograph for “Human Anti-D Immunoglobulin”), or
- intravenous administration¹ (and therefore comply with the Ph. Eur. monograph for “Human Anti-D Immunoglobulin for Intravenous Administration”).

Requirements for intravenous products which are additional to those for intramuscular preparations include tests and limits for anti-complementary activity and for anti-A and anti-B haemagglutinins.

The products are obtained from the pooled plasma of donors with sufficient titres of anti-D antibodies. Screening includes tests for the absence of markers for hepatitis B virus (HBV), hepatitis C virus (HCV) and human immunodeficiency virus (HIV), and an upper limit of 10⁴ IU/ml is applied at pool level for B19 virus DNA. Manufacture includes validated purification and virus inactivation/removal steps.

The labelling states the content of anti-D immunoglobulin in international units (IU) per container.

Since 1966, it has been accepted that Rh(D) immunisation following pregnancy 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. Recommendations from WHO working groups in 1967 and 1970 were adopted in a number of countries where haemolytic disease of the new-born (HDN) caused by anti-D antibodies was a significant cause of perinatal mortality and morbidity. Review and results of such programmes

¹ Intravenous preparations may, depending on the product, also be indicated for intramuscular administration.

were summarised and presented at the McMaster Conference on prevention of Rh(D) immunisation in September 1977, by Bowman in 1978 and 1985 and in a Technical Bulletin of the American College of Obstetricians and Gynaecologists in 1992. Consensus Conferences were held in Edinburgh and Switzerland in 1998, at which recommendations were reviewed and updated.

Whilst Anti-D immunoglobulins are licensed in Member States of the European Union, indications, dosage and methods of administration differ as a result of divergent clinical practice in individual Member States. This should be taken into account when clinical trials are designed.

This guideline describes the information to be documented when an application for a marketing authorisation for an anti-D immunoglobulin preparation is made, including biological data, clinical trials and patient follow up. These data are required for:

1. products for which an application for a marketing authorisation is to be submitted, referred to as "new products" in the text and
2. authorised products where a significant change in the manufacturing process has been made (e.g. additional viral inactivation/removal steps or new purification procedures).

The clinical trials described in this guideline should be performed according to the ICH Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95).

4.1.1 Clinical use

The well established indication of anti-D immunoglobulin is for the prevention of Rh(D) isoimmunisation in Rh(D) negative individuals challenged with Rh(D) positive erythrocytes e.g.

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.

The dosage of anti-D immunoglobulin is determined according to the level of exposure to Rh(D) positive blood, and has been 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.

Clinical efficacy in these indications cannot be examined using classical principles of clinical trials. Therefore, surrogate markers should be measured using appropriate methods and time intervals, e.g. 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. Not all dosage ranges used in clinical practice in the EU are expected to be studied in clinical trials. If the doses administered in the clinical trials are within the ranges given under 4.2 in the core SPC, then these ranges are to be adopted for the product specific SPC. However, the doses used in the trials are to be mentioned in section 5.1. The doses used in the clinical trials are thus considered a proof of principle.

Indications other than those listed above cannot be granted without relevant clinical data, including controlled clinical trials. In such cases, an SPC relevant to the use of the product in the specific indication will be required.

4.1.2 Safety

4.1.2.1 Adverse Events

All adverse events in clinical studies must be recorded and analysed with regard to causality, seriousness and expectedness. A detailed protocol of the studies specifying the methods for collection, intervals for collection of the data and duration of follow up is requested.

4.1.2.2 Viral safety

Manufacturers of plasma-derived products, including Anti-D immunoglobulin, are obliged to optimise viral safety by selection of donors, screening of individual donations and plasma pools for specific markers of infection and the inclusion of effective steps for the inactivation/removal of viruses in manufacturing processes.

The above-mentioned procedures are now considered to be highly effective and demonstrative of the viral safety of the product with respect to enveloped viruses. Therefore it is no longer considered appropriate to use clinical trials to investigate viral safety with regard to enveloped viruses.

These procedures may be of limited value against non-enveloped viruses, such as hepatitis A virus and parvovirus B19. The safety of the products with respect to non-enveloped viruses cannot currently be adequately evaluated in clinical studies.

The applicant is nevertheless required to provide all available data gathered on patients treated with the product in clinical trials. Investigators should continue with their normal clinical practice of monitoring patients. The applicant should demonstrate that there are systems in place to collect information on patients treated with the product and to respond rapidly to any reports of infection with a full investigation.

For products with an entirely novel manufacturing process other principles may apply. These applications should be discussed with the Regulatory Authorities prior to submission.

4.2. PRODUCTS FOR WHICH AN APPLICATION FOR A MARKETING AUTHORISATION IS TO BE SUBMITTED: “NEW PRODUCTS”

4.2.1 Biological, pharmacodynamic and pharmacokinetic data

4.2.1.1 Biological (cross reference to relevant Module 3)

The necessary data should be provided in Module 3 of the dossier. However, the following data relating to the pharmacodynamic and therapeutic activities and safety profile should also be provided in Part IV, with cross reference to the relevant sections in Module 3.

- *In vitro* potency assays addressing red cell destruction to assess product comparability
- Antibody content against different Rh(D) erythrocytes (R1R1, R1R2, R2R2)
- *In vivo* and/or *in vitro* quantification of anti-D antibodies
- IgG subclasses, in particular IgG₁ and IgG₃

4.2.1.2 Pharmacodynamics/pharmacokinetics

These data are essential to support the pharmacological activity and efficacy of the product, and must be provided in each application dossier.

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.

4.2.2 Efficacy

4.2.2.1 Prevention of Rh(D) isoimmunisation

Clinical data should be provided to demonstrate the efficacious prevention of Rh(D) isoimmunisation in Rh(D) negative women who are pregnant with a Rh(D) positive fetus (including D, D^{weak}, D^{partial}). The study should investigate at least 200 non-immunised patients and should include both ante-partum and post-partum administration, depending on the circumstance and indication for use, and should utilise an 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.

4.2.3 Safety

4.2.3.1 Adverse Events

Adverse events from all subjects followed in clinical studies should be recorded and reported in accordance with the ICH Guidelines on "Structure and content of clinical study report", CPMP/ICH/137/95 E3.

4.2.3.2 Viral safety

Compliance with CHMP recommendations with regard to viral safety under 4.1.2.2 above is necessary for all plasma derived products and is verified by information supplied in Module 3 of the dossier.

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

4.3. CHANGE IN THE MANUFACTURING PROCESS OF AUTHORISED PRODUCTS

Changes in the manufacturing procedures may lead to significant changes in the product and may thereby alter the structure of the immunoglobulin and its activity.

4.3.1 Biological, pharmacodynamic and pharmacokinetic data

4.3.1.1 Biological

The effects of changes in the manufacturing process (e.g. viral inactivation steps or new purification procedures) on the biological characteristics and activity of the product should be investigated. If significant impact on the activity of the immunoglobulin cannot be excluded, data on pharmacokinetics, efficacy and safety should also be provided with the application.

The necessary data should be provided in Module 3 of the dossier. However, the following data relating to pharmacodynamic and therapeutic activities and safety profile should also be provided in Module 5, with cross reference to the relevant sections in Module 3.

- *In vitro* potency assays addressing red cell destruction to assess product comparability
- Antibody content against different Rh(D) erythrocytes (R1R1,R1R2,R2R2)
- *In vivo* and /or *in vitro* quantification of anti-D antibodies
- IgG subclasses, in particular IgG₁ and IgG₃

4.3.1.2 Pharmacodynamics/Pharmacokinetics

Evidence should be provided that the change in the manufacturing process has not affected the pharmacokinetics of the product. Single dose studies should be carried out in 15 Rh(D) negative subjects, using the appropriate route of administration. Serum clearance, volume of distribution, area under the curve, mean serum half-life (α and β) should be measured. Results should be compared to those of parent product.

4.3.2 Efficacy

For products for which biological, pharmacokinetic and immediate safety data show no change from the parent product, no further clinical trials data are required.

4.3.3 Safety

4.3.3.1 Adverse events

As required for the parent product. (See 4.2.3.1)

4.3.3.2 Viral safety

Requirements for viral safety are the same as for the parent product. (See 4.1.2.2 and 4.2.3.2).