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Recommendations of the Executive Steering Group on Shortages and Safety of Medicinal Products to address anti-D immunoglobulin supply chain vulnerabilities

1. Introduction

Human anti-D immunoglobulin (anti-D Ig) medicinal products are currently the only available prophylactic medicine in Europe used for the prevention of Rhesus D (RhD) immunisation in pregnant women. RhD immunisation may occur during pregnancy of a RhD-negative woman with a RhD positive foetus where antibodies directed against red cell surface antigens may be developed. These allo-antibodies can cross the placenta and can cause the destruction of foetal red cells which can lead to haemolytic disease of the foetus and newborn, and, in severe cases, hydrops fetalis or severe hyperbilirubinemia and kernicterus.

Anti-D immunoglobulin is indicated for antenatal and postnatal prophylaxis as well as for the treatment of RhD negative childbearing age women after incompatible transfusions of RhD positive blood or other products containing red blood cells[1,2] (Annex).

Anti-D immunoglobulin is included in the Union list of critical medicines which identifies medicines for human use for which continuity of supply in the EU is a priority and shortages should be avoided, as these products are critical for EU healthcare systems to function properly.

Plasma containing the anti-D antibody is currently the only source for manufacturing anti-D Ig and can be obtained from (a) persons already immunised by pregnancy or transfusion and adequate anti-D (anti-Rho) antibody titres or (b) deliberately immunised volunteers[3].

[1] Core summary of products characteristics for human anti-D immunoglobulin for intramuscular use - Scientific guideline

[2] Core summary of product characteristics for human anti-D immunoglobulin for intravenous use - Scientific guideline

[3] Unknown author (1967). The suppression of Rh immunization by passively administered human immunoglobulin (IgG) anti-D (anti-Rh). Bulletin of the World Health Organization, 36 (3), 467 - 474. World Health Organization.

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In order to obtain and/or maintain high titre of anti-D Ig, hyperimmunisation of donors may be necessary, taking into consideration regulatory, safety, legal and ethical aspects[4].

In the past, several EU/EEA countries established national programs for the collection of plasma used for the manufacture of anti D Ig. At present, there is no plasma collection program in EU/EEA countries for the purpose of manufacturing anti-D Ig[5].

The following key vulnerabilities in the supply chain of anti-D Ig have been identified:

- Limited number of immunised donors and decline in the pool of existing donors.
- Challenges related to the collection, manufacturing and pooling of small plasma batches.
- Global supply capacity constraints with a limited number of Marketing Authorisation Holders and centres collecting plasma for the manufacture of anti-D Ig.
- High dependency on countries located outside of the EU/EEA for the supply of plasma for the manufacturing of anti-D IgG and finished plasma derived anti-D medicinal products.

The Executive Steering Group on Shortages and Safety of Medicinal Products (MSSG)[6], through the Medicine Shortages Single Point of Contact Working Party (SPOC WP), has being monitoring the availability, constraints and vulnerabilities of the supply chain of anti-D Ig. The identified vulnerabilities in the supply chain of anti-D Ig would require long-term multifactorial policy measures outlined in these recommendations.

Based on the MSSG recommendations to strengthen supply chains of critical medicinal products[7] published in April 2024, the MSSG is now proposing measures to address vulnerabilities in the supply chain of anti-D Igs.

While the recommendations address anti-D Ig supply chain vulnerabilities, the principles may also be applicable to address vulnerabilities in the supply chain of other Plasma Derived Medicinal Products (PDMPs) as outlined in the SUPPLY project[8] focussed on strengthening voluntary non-remunerated plasma collection capacity in Europe.

[4] Activities should be performed in compliance with applicable guidance on regulatory, safety, legal, ethical aspects:
- including relevant legislation, e.g. Regulation (EU) 2024/1938 of the European Parliament and of the Council of 13 June 2024 on standards of quality and safety for substances of human origin intended for human application and repealing Directives 2002/98/EC and 2004/23/EC (Text with EEA relevance)
- including ICH E9 (R1) addendum on estimands and sensitivity analysis in clinical trials to the guideline on statistical principles for clinical trials
- including ICH E6 Good clinical practice
- including the Guide for research ethics committee members (Guide for research ethics commitee members - Human Rights and Biomedicine)
- including Guide for the implementation of the principle of prohibition of financial gain with respect to the human body and its parts from living or deceased donors

[5] Local collection might be performed

[6] Regulation (EU) 2022/123 of the European Parliament and of the Council of 25 January 2022 on a reinforced role for the European Medicines Agency in crisis preparedness and management for medicinal products and medical devices (Regulation (EU) 2022/123)

[7] MSSG recommendations to strengthen supply chains of critical medicinal products

[8] Supply Project - Strengthening plasma collection capacity in Europe

2. Recommendations

2.1. Recommendations to Member States

- Member States are encouraged to develop action plans to secure the supply of anti-D Ig in the Union, based on the principles agreed at EU level, coordinated by the European Commission. Member States should also consider the involvement of relevant learned societies. These plans should be in compliance with relevant regulatory, safety, legal and ethical aspects[4]. These national action plans should explore, develop and implement effective mechanisms to enable plasma collection. In particular Member States should:
  - Describe and assess the clinical need in the use of anti-D immunoglobulins;
  - Assess and optimise strategies for non-invasive prenatal screening methods to avoid unnecessary use of anti-D immunoglobulins;
  - Consider appropriate pathways to establish anti-D plasma collection programmes, on the basis of regulatory, safety, legal and ethical frameworks[4];
  - Consider national guidance and existing best practices, including from jurisdictions outside of the Union;
  - Consider ownership of plasma and appropriate contract manufacturing strategies in this regard, where applicable;
  - Facilitate cooperation between the different sectors.
- Member States should put in place adequate measures to ensure that the collected plasma is of the best quality with high IgG titre while ensuring donor protection.
- Member States should establish safeguards to ensure that appropriate and sufficient fractionation and manufacturing capacities are available and thus ensure the adequate supply of anti-D Ig in Europe.
- Member States should identify solutions, including funding mechanisms, to support development and validation of alternatives to plasma derived anti-D immunoglobulins and foster research and development of innovative solutions to address identified vulnerabilities in the supply chain[4].
- Member States, in collaboration with experts, including learned societies, patient organisations, and other relevant stakeholders should develop national guidelines to facilitate prioritisation of patients who require these medicines during shortage situations, where necessary. The MSSG may coordinate the development of a Union level prioritisation plan to manage critical shortages, coordinated at Union level.
- In cases of critical shortages of medicinal products, national competent authorities concerned should inform the SPOC WP and consider the application of regulatory flexibilities where appropriate[9].
- Member States should implement communication and education strategies to increase awareness on plasma collection and utilisation for the development of plasma derived medicinal products, such as anti-D Ig.

2.2. Recommendations to the European Commission

The European Commission is encouraged to identify policy measures to ensure supply continuity of plasma and PDMPs, in particular with respect to security of supply of anti-D Ig in the EU. Where

[9] such as those detailed in the MSSG Toolkit on recommendations on tackling shortages of medicinal products or those outlined in Procedural Advice on Zero-day MR procedure (CMDh/451/2024).

necessary and to ensure a harmonised EU level approach, the European Commission should support and coordinate Member States' activities. This could include the following measures:

- To support Member States activities to explore and develop effective mechanisms for plasma collection, taken into account, regulatory, safety, legal, ethical guidance[4] and the policy measures set out in the proposed Critical Medicines Act, such as strategic projects focusing on increasing capacity for collecting active substance such as plasma;
- To facilitate cooperation between key stakeholders, including national competent blood authorities and national competent medicines authorities to ensure coherence across relevant legislative frameworks;
- To support Member States in identifying measures to optimise the use of anti-D Ig and develop national action plans and maximise the utilisation of plasma collected in Europe including the pooling of plasma used for the manufacture of anti-D Ig from one Member State or different Member States[10,11]. The proposed Critical Medicines Act includes provisions on joint procurement that could be used for certain manufacturing services, to establish or increase supply of anti-D Ig to the EU. In addition, the environmental impact linked to the manufacturing of anti-D Ig of the implementing measures should be considered;
- To support Member States in identifying policy solutions, including funding mechanisms, to support the development, validation and authorisation of alternatives to plasma derived anti-D immunoglobulins and foster research and development of innovative solutions to address identified vulnerabilities in the supply chain.

2.3. Recommendations to the plasma industry and relevant research organisations

The plasma industry and relevant research organisations should:

- Ensure that appropriate and sufficient fractionation and manufacturing capacities are available and thus ensure the adequate supply of anti-D Ig in Europe;
- Invest in research, development and validation of alternatives to plasma derived anti-D Ig and develop and implement innovative solutions to address identified vulnerabilities in the supply chain, taken into account regulatory, safety, legal and ethical aspects[4];
- Collaborate with Member States and the European Commission to identify effective mechanisms to support plasma collection and use. Consider initiatives and tools implemented by regulatory authorities to secure the supply of anti-D immunoglobulins and where needed, provide relevant data necessary for identifying and developing these mechanisms.

[10] Directive 2001/83/EC, as amended (EUR-Lex - 02001L0083-20220101 - EN - EUR-Lex)

[11] EudraLex The Rules Governing Medicinal Products in the European Union Volume 4 EU Guidelines for Good Manufacturing Practice for Medicinal Products for Human and Veterinary Use Annex 14 Manufacture of Medicinal Products Derived from Human Blood or Plasma

3. Annex

The therapeutic indications for the medicinal products according to the guidelines on the core Summary of Product Characteristics (SmPC) for human and-D immunoglobulin for intramuscular and intravenous use are:

- 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, Dweak, Dpartial) 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.