LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Rhesonativ
(Human anti-D immunoglobulin)

SE/H/541/02/DC

This module reflects the scientific discussion for the approval of Rhesonativ. The procedure was finalised on 2017-07-06. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

Octapharma AB has applied for a marketing authorisation for Rhesonativ, 750 IU/ml, solution for injection (new strength). The active substance human anti-D immunoglobulin is the same as in Rhesonativ, 625 IU/ml, solution for injection, marketed by Octapharma AB since 1976.

For approved indications, see the Summary of Product Characteristics.

The marketing authorisation has been granted pursuant to Article 8(3), known active substance, of Directive 2001/83/EC.

For recommendations to the marketing authorisation not falling under Article 21a/22 of Directive 2001/83 and conditions to the marketing authorisation pursuant to Article 21a or 22 of Directive 2001/83/EC to the marketing authorisation, please see section VI.

II. QUALITY ASPECTS

II.1 Introduction

Rhesonativ is presented in the form of a solution for injection containing 165 mg/ml human immunoglobulin which corresponds to 750 IU/ml of human anti-D immunoglobulin. The excipients are glycine, sodium acetate, sodium chloride and water for injection. The solution is filled in ampoules of colourless glass.

II.2 Drug Substance

Since the drug substance human anti-D immunoglobulin is isolated during the manufacture of the final product, the manufacturing process from plasma to final product is covered below under the heading Medicinal Product.
Regarding the quality of the starting material, human plasma, the Octapharma Plasma Master File (PMF) has been certified by EMA with the number EMEA/H/PMF/000008. The certified PMF covers the information about the measures put in place to prevent infections being passed on to patients from the starting material, such as careful selection of blood and plasma donors, testing of each donation and pools of plasma for signs of virus/infections.

II.3 Medicinal Product

The medicinal product is formulated using excipients listed in section 6.1 in the Summary of Product Characteristics. The excipients are described in the current PhEur.

The manufacturing process has been sufficiently described and critical steps identified. Results from the process validation studies confirm that the process is under control and ensure both batch to batch reproducibility and compliance with the product specification.

The tests and limits in the specification are in compliance with the European Pharmacopoeia monographs for Human anti-D Immunoglobulin and Human Normal Immunoglobulin and are considered appropriate to control the quality of the finished product in relation to its intended purpose.

Stability studies have been performed and data presented support the shelf life and special precautions for storage claimed in the Summary of Product Characteristics, sections 6.3 and 6.4.

With regard to measures taken to prevent transmission of infections resulting from the use of human blood or plasma, satisfactory reduction of viruses has been demonstrated for the production process. Effective reduction of enveloped viruses such as HIV, hepatitis B and hepatitis C has been shown as well as significant reduction of non-enveloped viruses such as hepatitis A virus. The process has shown limited efficacy in reducing the non-enveloped parvovirus B19 as this virus may be present in very high titres in human plasma. Therefore, it is stated in the SPC (under point 4.4) that the inactivation/elimination procedures may be of limited value against certain non-enveloped viruses such as parvovirus B19. There is however reassuring clinical experience regarding the lack of hepatitis A virus and parvovirus B19 transmission with immunoglobulins and it is also assumed that the antibody content in the finished product makes an important contribution to the viral safety. Furthermore, as required by the European Pharmacopeia parvovirus B19 DNA is tested by NAT with a cut-off limit of ≤10 IU/µl (=4 $\log_{10}$ IU/ml), which also contribute to the viral safety of the product.

Compliance with Commission Directive 2003/63/EC and the NfG on Minimising the risk of transmitting Animal Spongiform Encephalopathy Agents via human and veterinary medicinal products (EMEA/410/01) has been declared by the company. No material used in the manufacturing of Rhesonativ originates from animal species susceptible to TSE.

III. NON-CLINICAL ASPECTS

The active substance human anti-D immunoglobulin is the same as in Rhesonativ, 625 IU/ml, solution for injection, marketed by Octapharma AB since 1976. There are no new non-clinical data presented within this application.

IV. CLINICAL ASPECTS

The active substance human anti-D immunoglobulin is the same as in Rhesonativ, 625 IU/ml, solution for injection, marketed by Octapharma AB since 1976. There are no new clinical data presented within this application.

IV.1 Risk Management Plans

The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Rhesonativ.

Safety specification

Summary table of safety concerns as approved in RMP version 0.3

Summary of safety concerns	
Important Identified Risks	- Hypersensitivity reactions, including anaphylactic reactions
Important Potential Risks	- Virus safety - Thrombogenicity (Embolic and thrombotic events) - Haemolytic reactions - Interference with serological testing
Missing Information	- Lack of efficacy in overweight/obese patients

Pharmacovigilance Plan

Routine pharmacovigilance is suggested and no additional pharmacovigilance activities are proposed by the applicant, which is endorsed.

Risk minimisation measures

Routine risk minimisation is suggested and no additional risk minimisation activities are proposed by the applicant, which is endorsed.

Summary of the RMP

The RMP is approved.

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the RMS;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time, but via different procedures.

V. USER CONSULTATION

A user consultation with target patient groups on the package information leaflet (PIL) has been performed on the basis of a bridging report making reference to Rhesonativ, Solution for injection (SE/H/541/01/E02). The bridging report submitted by the applicant has been found acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The benefit/risk ratio is considered positive and Rhesonativ, 750 IU/ml, solution for injection is recommended for approval.

List of recommendations not falling under Article 21a/22 of Directive 2001/83 in case of a positive benefit risk assessment

N/A

List of conditions pursuant to Article 21a or 22 of Directive 2001/83/EC

N/A

VII. APPROVAL

The Decentralised procedure for Rhesonativ, 750 IU/ml, solution for injection was positively finalised on 2017-07-06.

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Public Assessment Report – Update

Procedure number*	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse

*Only procedure qualifier, chronological number and grouping qualifier (when applicable)

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