LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Rhesonativ
(Human anti-D immunoglobulin)

SE/H/541/01

This module reflects the scientific discussion for the approval of Rhesonativ. The procedure was finalised at 6/3 2006. For information on changes after this date please refer to the module 'Update'.

I. INTRODUCTION

Octapharma has applied for a marketing authorisation for Rhesonativ, solution for injection, 625 IU/ml. The active substance human anti-D immunoglobulin is isolated and purified from a pool of human plasma with a high level of anti-D antibodies.

Rhesonativ is indicated for:
Prevention of Rh(D) immunisation in Rh(D) negative women.

- *Pregnancy/delivery of a Rh-positive baby.*
- *Abortion/threatened abortion, ectopic pregnancy or hydatidiform mole.*
- *Transplacental haemorrhage (TPH) resulting from ante-partum haemorrhage (APH), amniocentesis, chorionic biopsy or obstetric manipulative procedures, e.g. external version, or abdominal trauma.*

Treatment of Rh(D) negative persons after incompatible transfusions of Rh(D) positive blood or other products containing red blood cells.

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 625 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 EMEA with the number EMEA/H/PMF/000008/05. 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

Rhesonativ, solution for injection, 625 IU/ml, is formulated using excipients 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 under ICH conditions have been performed and data presented support the shelf life claimed in the SPC, when stored in a refrigerator (2°C-8°C).

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 or parvovirus B19 transmission with immunoglobulins and it is also assumed that the antibody content 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

IgG is a normal constituent in human plasma. IgG has not been reported to be associated with any embryo-foetal toxicity or oncogenic /carcinogenic potential. Furthermore there are a broad knowledge and a vast clinical experience of human IgG. Rhesonativ contains a specified minimum amount of anti-D immunoglobulins. The pharmacology and toxicology of these specific antibodies can only be addressed clinically. This is true for the main safety issue, as identified in the Non-clinical Overview: anti-D antibodies can cross the placenta and raise fetal antibody titres, thereby increasing the potential risk of haemolytic damage to RhD positive fetuses. However, published clinical data show no evidence for such effect.
The manufacturing of the product and the specifications comply with the European Pharmacopoeia and the toxicity profile of the impurity TNBP is considered adequately characterized. There are no preclinical concerns with this product since the level of TNBP is well below the limits where any toxicity may be expected.

IV. CLINICAL ASPECTS

IV.1 Pharmacokinetics

The pharmacokinetics of Rhesonativ was investigated in 15 Rh-negative women in the 28th week of gestation and in 3 non-pregnant women. The mean half-lifes of anti-D were 24 days (range 16-30) and 21 days (17-24) in women with Rh-negative and Rh-positive infants respectively. The maximal concentrations after i.m. injection of 125µg Rhesonativ in pregnant women was 8 ng/ml and 16 ng/ml after 250 µg.

IV.2 Pharmacodynamics

The effect of Rhesonativ on Rh-immunisation after injection of Rh-positve fetal red cells to 21 Rh-negative volunteers was studied.
The volunteers were injected with Rh–positive, ABO-compatible fetal red cells in amounts corresponding to 10 mL cord blood (1 case), 25 mL (10 cases) and 50 mL (10 cases).
Two to 3 days later 260 µg of Rhesonativ were given intramuscularly (i.m.). Six months later no serologic evidence for Rh–immunization was found in any individual. From these experimental findings it was concluded that Rh–prophylaxis is achieved with 10 µg of anti–D immunoglobulin per mL of fetal blood.

IV.3 Clinical efficacy

In total, 8 clinical trials with Rhesonativ were conducted between 1968 and 1997. One of these studies was the transfusion study cited above. In one study the efficacy and safety of antenatal prophylaxis was investigated in 529 pregnant women.
The remaining six studies investigated post-partum prophylaxis in more than 6000 patients with a reported efficacy rate of 0-0.4% seroconversions (in follow-up usually at 6 months).
The dose used was 250 µg Rhesonativ in a single i.m.dose.
Although the clinical studies with Rhesonativ were carried out before the introduction of the guidelines, the extent of the clinical data are essentially in line with the recommendations.

IV.4 Clinical safety

No adverse events were reported in any of the clinical studies.
Between 1996 and 2004 (earlier sales figures are not available) a total amount of about 188.8 million IU of Rhesonativ has been sold. The total number of patients exposed during this period is estimated to be about 95,000. In the post-marketing phase, seven non-serious adverse reactions have been reported.
The safety of Rhesonativ is judged to be sufficiently covered by clinical studies and post-marketing experience. It should be noted, however, that minor complications, e.g. administration site reactions, probably are under-reported in the clinical studies that were performed before the introduction of modern GCP principles. However, the extensive clinical experience with this product without reported serious adverse reactions is deemed to be reassuring.

V. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The risk/benefit ratio is considered positive and *Rhesonativ, 625 IU/ml, solution for injection* is recommended for approval.

User testing of the package leaflet has not been performed. The applicant has made a commitment to perform user testing. The results of consultation with target patient groups will be submitted in a type II variation before marketing.

The current core SPC for human anti-immunoglobulin D is currently under revision. The applicant commits to update the SPC in line with the revised core SPC when finalised.