Viral Inactivation and Removal

<table>
<thead>
<tr>
<th>Virus</th>
<th>HIV</th>
<th>BVDV</th>
<th>PRV</th>
<th>MVM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genome</td>
<td>RNA</td>
<td>RNA</td>
<td>DNA</td>
<td>DNA</td>
</tr>
<tr>
<td>Envelope</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Size</td>
<td>80–100 nm</td>
<td>40–70 nm</td>
<td>120–200 nm</td>
<td>18–24 nm</td>
</tr>
<tr>
<td>S/D-treatment</td>
<td>≥ 6.0</td>
<td>≥ 5.4</td>
<td>≥ 5.6</td>
<td>Not tested</td>
</tr>
<tr>
<td>Chromatographic process steps</td>
<td>4.5</td>
<td>1.6</td>
<td>≥ 3.9</td>
<td>≥ 2.6</td>
</tr>
<tr>
<td>Nanofiltration</td>
<td>≥ 6.3</td>
<td>≥ 5.5</td>
<td>≥ 5.6</td>
<td>3.4</td>
</tr>
<tr>
<td>Overall reduction (log10 units)</td>
<td>≥ 16.8</td>
<td>≥ 12.5</td>
<td>≥ 15.1</td>
<td>≥ 6.0</td>
</tr>
</tbody>
</table>

HIV: Model for HIV-1 and HIV-2.
BVDV: Bovine viral diarrhea virus, as a model for HIV.
PRV: Pseudorabies virus, as a model for large, enveloped DNA viruses (e.g., herpes virus).
MVM: Minute virus of mice, as a model for parvovirus B19 and parvovirus B19.

Rhophylac® is produced by an ion-exchange chromatography isolation procedure, using pooled plasma obtained by plasmapheresis of immunized Rh(D)-negative US donors. The manufacturing process includes a solvent detergent (S/D) treatment step (using tri-n-butyl phosphate and Triton® X-100) that is effective in inactivating enveloped viruses such as HBV, HCV, and HIV. Rhophylac® is nanofiltered using a Planova® 15 nm virus filter which has been validated to be effective in the removal of enveloped as well as non-enveloped viruses. Viral clearance and inactivation data from validation studies are presented below.

The donor selection criteria, testing of donations and manufacturing pools, together with purification steps and specific viral inactivation and removal steps are included to ensure the safety of this product with respect to potential contamination with blood borne pathogens.
been transmitted by this product should be reported by the physician or other healthcare provider to ZLB Bioplasma Inc. at (888) 244 2952. The physician should discuss the risks and benefits of this product with the patient.

PRECAUTIONS

For postpartum use, Rhophylac® is intended for maternal administration. It should not be given to the newborn infant. The product is not intended for use in Rh(D)-positive individuals. Patients should be observed for at least 20 minutes after administration.

As with all pharmaceutical agents, allergic responses may occur. If symptoms of allergic or anaphylactic type reactions occur, immediately discontinue administration. Patients should be informed of the early signs of hypersensitivity reactions including hives, generalized urticaria, tightness of the chest, wheezing, hypotension and anaphylaxis. The treatment required depends on the nature and severity of the side effect. If necessary, the current medical standards for shock treatment should be observed.

The concentration of IgA in Rhophylac® was found to be below the detection limit of 5 µg/mL. Nevertheless, the product may contain trace amounts of IgA. Although anti-D immunoglobulin has been used to treat selected IgA deficient individuals, the attending physician must weigh the benefit against the potential risk of hypersensitivity reactions. Individuals deficient in IgA have a potential for development of IgA antibodies and anaphylactic reactions after administration of blood components containing IgA.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. The solution should be clear or slightly opalescent. Do not use solutions that are cloudy or have deposits.

Drug Interactions

Active immunization with live virus vaccines (e.g., measles, mumps, rubella or varicella) should be postponed until 3 months after the last administration of immunoglobulin products, as the efficacy of the live virus vaccine may be impaired. If immunoglobulin needs to be administered within 2–4 weeks of a live virus vaccination, then the efficacy of such a vaccination may be impaired. The results of blood typing and antibody testing in neonates, including the Coombs or antigen level test, may be affected by the administration of anti-D immunoglobulin.

Rhophylac® can contain antibodies to other Rh antigens, e.g., anti-C antibodies, which might be detected by sensitive serological test methods following administration of the product.

Pregnancy Category C

This medicinal product is used in pregnancy. Animal reproduction studies have not been conducted with Rhophylac®. The available evidence suggests that Rhophylac® does not harm the fetus or affect future pregnancies or the reproduction capacity of the maternal recipient.

Rh(D) Immune Globulin is not secreted in breast milk. No hazards are expected during breast-feeding.

ADVERSE REACTIONS

When anti-D immunoglobulins are administered by the intramuscular route, local pain and tenderness can be observed at the injection site; this can be prevented by dividing larger doses over several injection sites.

Mild and transient fever, malaise, headache, cutaneous reactions and chills occur occasionally. Parenteral injection products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. The solution should be clear or slightly opalescent. Do not use solutions that are cloudy or have deposits.

In case of known or suspected excessive feto-maternal hemorrhage, the number of fetal red blood cells in the maternal circulation should be determined. If excess transplacental bleeding is measured, extra anti-D immunoglobulin (110 IU [20 µg] for each 1 mL of fetal red blood cells) should be administered, preferably by the intravenous route. If testing is not feasible and an excessive feto-maternal hemorrhage cannot be excluded, a further 1500 IU (300 µg) should be administered. A 1500 IU (300 µg) dose will suppress the immunizing potential of at least 15 mL of Rh(D)-positive red blood cells.

Rhophylac® should be administered by intravenous or intramuscular injection as soon as possible within 72 hours of delivery, or of the at-risk event, in cases of obstetric complications or invasive procedures.

For incompatible transfusions, the recommended dose is 100 IU (20 µg) anti-D IgG per 2 mL of transfused Rh(D)-positive blood or per 1 mL of Rh(D)-positive erythrocyte concentrate.

Rhophylac® should be brought to room or body temperature before use. Rhophylac® should be administered by slow intravenous or by intramuscular injection. If large doses (> 5 mL) are required and intramuscular injection is chosen, it is advisable to administer them in divided doses at different sites. Rhophylac® is for single use only. Any unused product or waste material should be disposed of in accordance with local requirements.

HOW SUPPLIED

Rhophylac®, Rh(D) Immune Globulin Intravenous (Human) 1500 IU (300 µg) is available in packages containing one or ten pre-filled 2 mL syringes.

STORAGE

Store at 2 °C to 8 °C (36 °F to 46 °F). If stored at this temperature, Rhophylac® has a shelf life of 36 months. Do not freeze. Protect from light. The preparation should not be used after the expiration date printed on the label.

REFERENCES


4. Data on file at ZLB Bioplasma AG.


6. Data on file at ZLB Bioplasma AG.


Distributed by: ZLB Bioplasma AG

Manufactured by:

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Switzerland
US License No. 1598

Distributed by:

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Glendale, California 91203, USA

Last Revision: January 2004

<table>
<thead>
<tr>
<th>Indication</th>
<th>Dose (administer IM or IV)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pregnancy</td>
<td>1500 IU (300 µg)</td>
</tr>
<tr>
<td>Postpartum prevention</td>
<td>1500 IU (300 µg)</td>
</tr>
<tr>
<td>Obstetric conditions</td>
<td>1500 IU (300 µg)</td>
</tr>
<tr>
<td>Incompatible transfusions</td>
<td>100 IU (20 µg) per 2 mL transfused blood or per 1 mL erythrocyte concentrate</td>
</tr>
</tbody>
</table>