FREQUENTLY ASKED QUESTIONS ABOUT THE USE OF RHOPHYLAC®

Abbreviations

Blood Service	Australian Red Cross Blood Service
TGA	Therapeutic Goods Administration
AUST R	Australian registration number
NBA	National Blood Authority
HIV	Human Immunodeficiency Virus
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HAV	Hepatitis A virus
FMH	Fetomaternal haemorrhage

Introduction

The answers to the following frequently asked questions are intended for use by healthcare professionals and have been prepared and endorsed by CSL Biotherapies and the Australian Red Cross Blood Service.

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A. GENERAL QUESTIONS

1.0 Product characteristics

1.1 What is RHOPHYLAC?

RHOPHYLAC is a human Anti-D (Rh_o) immunoglobulin solution for injection presented in a pre-filled syringe. Each RHOPHYLAC pre-filled syringe contains 2mL or 1500 IU (300µg) human Anti-D immunoglobulin, corresponding to a concentration of 750 IU (150µg) per mL.

RHOPHYLAC is manufactured at CSL Behring AG Bern, Switzerland. It is manufactured from plasma collected from US donors at Therapeutic Good Administration (TGA) and Food and Drug Administration (FDA) approved blood centres. The manufacturing process for RHOPHYLAC uses ion exchange chromatography which not only helps minimize the risk of viral transmission, but also allows for very high purity by eliminating virtually all foreign aggregates from the source plasma and therefore allows for both intravenous (IV) and intramuscular (IM) administration.

RHOPHYLAC was approved by the TGA in Australia on 1 September 2009 as an alternative source of Rh (D) immunoglobulin for intravenous administration. In March 2011, the NBA approved the supply of RHOPHYLAC within Australia when access to an intravenous Rh (D) immunoglobulin is required.

References:

1. RHOPHYLAC Product Information, date of TGA approval 01 September 2009

2.0 Supply

2.1 For what clinical indications will RHOPHYLAC be supplied?

In March 2011, the NBA approved the supply of RHOPHYLAC within Australia when access to an intravenous Rh (D) immunoglobulin is required. RHOPHYLAC is indicated for use in large fetomaternal haemorrhage (FMH) where administration of intramuscular Rh (D) immunoglobulin is either contraindicated or not practical, or for inadvertent or emergency transfusion of Rh (D) positive blood to an Rh (D) negative female of childbearing potential.

Specifically, RHOPHYLAC is not authorised for use in immune thrombocytopenic purpura (ITP) within Australia.

References:

1. RHOPHYLAC Product Information, date of TGA approval 01 September 2009

2.2 Why are we receiving RHOPHYLAC?

RHOPHYLAC is available in reserve for when access to an intravenous Rh (D) immunoglobulin is warranted. Previously, intravenous Rh(D) immunoglobulin supply was ensured with the product, WinRho-SDF (Baxter). Supply of WinRho-SDF will be phased out and replaced by RHOPHYLAC.

2.3 How can I access RHOPHYLAC?

RHOPHYLAC can be accessed via the Blood Service when an intravenous Rh (D) immunoglobulin preparation is required. Contact the Blood Service Transfusion Medicine Specialist in your capital city.

2.4 Why are we receiving RHOPHYLAC with English International packaging and Product Information?

One introductory batch of RHOPHYLAC (Batch 4345200052) will be supplied with the English version of the International packaging (carton and label) and Product Information (PI) for a short time period due to the need to ensure continuity of supply of intravenous Rh (D) immunoglobulin.

CSL have received an exemption from the TGA to import RHOPHYLAC with the International packaging and associated Product Information. It is anticipated that RHOPHYLAC with the Australian approved packaging and Product Information will be supplied from September 2011. The RHOPHYLAC batch supplied with the International packaging is the same product as that which will be supplied with Australian packaging.

The main difference between the RHOPHYLAC International packaging and the Australian approved packaging is the way the dose is presented. The dose on the International packaging is expressed as 300µg, whereas it is 1500 IU on the Australian approved packaging. A 300µg dose is equivalent to 1500 IU. The indications, dosing and administration instructions are the same for both versions of the product.

The batch supplied with International packaging will have a label detailing the AUST R number and the CSL Biotherapies contact details applied to the product carton.

References:

1. RHOPHYLAC English International Package Insert, date of revision of the text, July 2007.

2. RHOPHYLAC Product Information, date of TGA approval 01 September 2009

3.0 Dose and Administration

For specific dose and administration information please refer to Section B - FETOMATERNAL HAEMORRHAGE SPECIFIC QUESTIONS or Section C –RH (D) INCOMPATIBLE TRANSFUSION SPECIFIC QUESTIONS

3.1 Can a part-dose of RHOPHYLAC be administered?

The RHOPHYLAC Product Information or Package Insert does not specifically refer to splitting a dose of RHOPHYLAC. However, this may be required in the event of large fetomaternal haemorrhages (>15 mL) where the recommended dose is 1500 IU (300µg) plus 100 IU (20µg) per mL of fetal red cells in excess of 15mL.

While no specific data is available regarding administering a dose above what is calculated, it is noted in the Package Insert that overdosage should not lead to more frequent or more severe undesirable effects than the normal dose. It is advised that patients in receipt of an Rh (D) incompatible transfusion should be monitored clinically and by biological parameters because of the risk of haemolytic reaction.

References:

1. *RHOPHYLAC Product Information, date of TGA approval 01 September 2009*
2. *RHOPHYLAC English International Package Insert, date of revision of the text, July 2007*

3.2 Why is the RHOPHYLAC dose 1500 IU rather than 600 IU or 625 IU?

RHOPHYLAC is formulated to allow a larger dose and intravenous administration in larger fetomaternal haemorrhages and Rh (D) incompatible transfusions.

RHOPHYLAC is supplied as a pre-filled 2mL syringe containing 1500 IU (300µg) human Anti-D immunoglobulin. A 1500 IU (300µg) dose of RHOPHYLAC will suppress the immunising potential of <15mL of Rh (D) positive red cells. Therefore, 100 IU (20µg) will suppress the immunising potential of 1mL of Rh (D) positive red cells. For other Rh (D) immunoglobulin products such as WinRho-SDF^{TM} (600 IU) and RhD Immunoglobulin-VF (625 IU), 100 IU also suppresses the immunising potential of 1mL of Rh (D) positive red cells.

Recommended doses of Rh (D) immunoglobulin vary internationally from 500 IU to 1500 IU. There are no comparative studies of one manufacturer's product versus another.

References:
1. RHOPHYLAC English International Package Insert, date of revision of the text, July 2007.
2. RHOPHYLAC Product Information, date of TGA approval 01 September 2009
3. WinRho-SDF Product Information, date of most recent amendment 06 May 2010
4. EMEA Guideline on the Core SPC for Human Anti-D Immunoglobulin for Intravenous Use – Revision 1 (CHMP/BPWP/319619/2005) 1 April 2008

3.3 Is RHOPHYLAC administered intravenously or intramuscularly?

RHOPHYLAC can be administered by intravenous or intramuscular injection. In the case of haemorrhagic disorders where intramuscular injections are contraindicated, RHOPHYLAC should be administered intravenously. If large doses (more than 5mL) are required and intramuscular injection is chosen, it is advisable to administer them in divided doses at different sites.

References:

1. RHOPHYLAC Product Information, date of TGA approval 01 September 2009

3.4 What is the infusion rate for RHOPHYLAC?

For intravenous administration, the recommended rate of infusion is 2mL (1500 IU) per 15 to 60 seconds. If multiple vials are required, it is recommended the maximum infusion rate is 2mL (1500 IU) per 60 seconds.

References:

1. RHOPHYLAC U.S. Package Insert. Date of Initial US Approval 2004. Revised 09/2010

4.0 Safety

4.1 Is RHOPHYLAC as safe as Rh (D) Immunoglobulin-VF fractionated by CSL Biotherapies?

The plasma used to manufacture RHOPHYLAC comes from US donors who are carefully screened and briefed about their responsibility and is collected at TGA and FDA approved blood centres. The quality assurance measures performed in the manufacture of RHOPHYLAC are comparable to those used by the Blood Service and CSL Biotherapies during the collection of plasma for and manufacture of Rh (D) Immunoglobulin-VF.

The pathogen safety measures in place for RHOPHYLAC include the careful selection of donors, screening of individual donations and plasma pools for specific markers of infection and the inclusion of effective manufacturing steps for the inactivation/removal of viruses. Solvent-detergent treatment and virus filtration clearance steps included in the manufacturing process ensure the viral safety of the product. The measures taken are considered effective for enveloped viruses such as HIV, HBV, and HCV and for the non-enveloped viruses HAV and parvovirus B19.

References:

1. *RHOPHYLAC Product Information, date of TGA approval 01 September 2009*
2. *Rh(D) Immunoglobulin-VF Product Information, date of most recent amendment 07 December 2007*

4.2 What adverse events may be associated with the administration of RHOPHYLAC?

The following reactions have been reported in clinical trials and post-marketing studies with RHOPHYLAC:

General Uncommon	 fever, chills, malaise, injection site swelling, tenderness and pain (IM)
Immunological Uncommon Rare	 transient positive anti-C antibody test anaphylactic reaction, anaphylactic shock
Neurological Uncommon	 headache, dizziness, vertigo
Gastrointestinal Uncommon Rare	 nausea, vomiting diarrhoea
Cardiovascular Rare	 hypotension, tachycardia
Respiratory Rare	 dyspnoea
Musculoskeletal Rare	 back pain
Skin Uncommon	 rash, erythema, pruritus

In clinical trials with RHOPHYLAC®**,** all adverse reactions were mild to moderate in intensity.

To report a suspected adverse reaction to any CSL Biotherapies plasma-derived product,

Phone: 1800 642 865

Fax: +61 3 9389 1095

E-mail: drugsafety@csl.com.au

References:

1. *RHOPHYLAC Product Information, date of TGA approval 01 September 2009*

5.0 Storage

5.1 What is the shelf life and recommended storage conditions for RHOPHYLAC?

RHOPHYLAC has a shelf life of 3 years (36 months) when stored at 2-8^{o}C and protected from light. It must not be frozen. Do not use after the expiry date.

References:

1. *RHOPHYLAC Product Information, date of TGA approval 01 September 2009*

6.0 Other

6.1 Does RHOPHYLAC contain thiomersal?

(Thiomersal is a mercury-based antibacterial preservative used in some products)

No, RHOPHYLAC does not contain Thiomersal.

References:

1. *RHOPHYLAC Product Information, date of TGA approval 01 September 2009*

6.2 Does RHOPHYLAC contain red blood cells?

No, RHOPHYLAC does not contain red blood cells.

References:

1. *RHOPHYLAC Product Information, date of TGA approval 01 September 2009*

6.3 Does RHOPHYLAC contain IgA?

RHOPHYLAC contains not more than 5µg/mL of IgA. The concentration of IgA in RHOPHYLAC was found to be below the detection limit of 5µg/mL. Nevertheless, the product may contain trace amounts of IgA. Although Rh (D) immunoglobulin has been used successfully to treat selected IgA deficient patients, individuals who are deficient in IgA have the potential for developing IgA antibodies and may have anaphylactic reactions after administration of blood components containing IgA. The treating physician must therefore weigh the benefit of treatment with RHOPHYLAC against the potential risks of hypersensitivity reactions.

References:

1. *RHOPHYLAC Product Information, date of TGA approval 01 September 2009*

B. FETOMATERNAL HAEMORRHAGE SPECIFIC QUESTIONS

7.0 Fetomaternal haemorrhages

7.1 What dose of RHOPHYLAC should be administered for FMH?

For prevention of Rh (D) sensitisation in Rh (D) negative women when an intravenous Rh (D) immunoglobulin preparation is required, a 1500 IU (300µg) dose of RHOPHYLAC will suppress the immunising potential of <15mL of Rh (D) positive red cells. For large fetomaternal haemorrhage (>15mL), 1500 IU (300µg) plus 100 IU (20µg) per mL of fetal red cells in excess of 15mL should be administered.

If a large fetomaternal haemorrhage (greater than 4mL) is suspected, e.g. in the event of fetal anaemia or intrauterine fetal death, its extent should be determined by a suitable method (e.g. Kleihauer-Betke test) and additional doses of Rh (D) immunoglobulin should be administered as outlined above.

RHOPHYLAC should always be administered within 72 hours of a potentially sensitising event. If Rh (D) immunoglobulin has not been offered within 72 hours, a dose offered within 9-10 days may provide protection. During the informed consent process, the patient should be advised of the potential consequences of the delay in the administration of Rh (D) immunoglobulin and consideration be given to insurer notification.

References:

1. *RHOPHYLAC Product Information, date of TGA approval 01 September 2009*
2. *National Blood Authority Guidelines on the prophylactic use of Rh (D) immunoglobulin (anti (D) in Obstetrics. June 2003.*

7.2 Will RHOPHYLAC be used for antenatal and postnatal prophylaxis?

The introduction of RHOPHYLAC will not affect the current *Guidelines for the Prophylactic Use of Rh (D) Immunoglobulin (Anti-D) in Obstetrics*. CSL Biotherapies Rh (D) Immunoglobulin-VF (for intramuscular administration) will remain the Rh (D) immunoglobulin product for all routine prophylaxis in pregnant women with Rh (D) negative blood group and no pre-existing anti-D antibodies.

The NBA has approved the supply of RHOPHYLAC within Australia when access to an intravenous Rh (D) immunoglobulin is required. Such indications include large fetomaternal haemorrhages or inadvertent or emergency transfusion of Rh (D) positive blood to an Rh (D) negative female of childbearing potential.

References:

1. *National Blood Authority Guidelines on the prophylactic use of Rh (D) immunoglobulin (anti-D) in obstetrics. June 2003*
2. *Rh (D) Immunoglobulin-VF Approved Product Information. Date of most recent amendment 07 December 2007*
3. *RHOPHYLAC Product Information, date of TGA approval 01 September 2009*

7.3 What are the major differences between Rh (D) Immunoglobulin-VF, RHOPHYLAC and WinRho-SDF?

Feature	Rh (D) Immunoglobulin-VF	RHOPHYLAC	WinRho-SDF
Viral Inactivation Steps	Pasteurisation & nanofiltration	Solvent detergent & virus filtration	Solvent detergent & virus filtration
Administration	Intramuscular only	Intravenous or Intramuscular	Intravenous or Intramuscular
Formulation	Liquid, ready to use	Ready to use, pre-filled syringe	Sterile freeze-dried vial and diluent
Presentation	250 IU, 625 IU	1500 IU (300µg)	600 IU
Volume	The actual volume in the vial is stated on the label	2mL	Reconstituted to 1.25mL to 2.5mL (480 IU/mL – 240 IU/mL) for intravenous administration
Use in Large FMH	NOT INDICATED	- 100 IU (20µg) RHOPHYLAC/mL Rh (D) positive red cells - A 1500 IU (300µg) vial will suppress the immunising potential of <15mL of Rh (D) positive red cells. - Maximum dose 15,000 IU (3000µg), independent of whether the transfusion volumes are >300mL of Rh (D) positive blood	- 100 IU (20µg) WinRho-SDF/mL Rh (D) positive red cells - A 600 IU (120µg) vial will suppress the immunising potential of <6mL of Rh(D) positive red cells - Maximum dose 3000 IU q8h IV
Administration (intravenous)	NOT APPLICABLE	- 2mL (1500 IU) per 15-60 seconds. For multiple vials, 2mL per 60 seconds.	- 1.25mL - 2.5mL (480 IU/mL – 240 IU/mL) injected into a suitable vein at a rate of 1500 IU

		- within 72 hours of complication	- within 72 hours of complication

References:

1. Rh(D) Immunoglobulin-VF Product Information, date of most recent amendment 07 December 2007

2. RHOPHYLAC Product Information, date of TGA approval 01 September 2009

3. WinRho-SDF Product Information, date of most recent amendment 06 May 2010

4. EMEA Guideline on the Core SPC for Human Anti-D Immunoglobulin for Intravenous Use – Revision 1 (CHMP/BPWP/319619/2005) 1 April 2008

5. RHOPHYLAC U.S. Package Insert. Date of Initial US Approval 2004. Revised 09/2010

C. RH (D) INCOMPATIBLE TRANSFUSION SPECIFIC QUESTIONS

8.0 Rh (D) incompatible transfusions

8.1 What dose of RHOPHYLAC should be administered for an Rh (D) incompatible transfusion?

For Rh (D) incompatible transfusions, the recommended dose for RHOPHYLAC is 100 IU (20µg) Rh (D) immunoglobulin per 2mL of transfused Rh (D) positive whole blood or 1mL of red cell concentrate. The intravenous route of administration is recommended. A maximum dose of 15,000 IU (3000µg) is sufficient in the case of larger incompatible transfusions independent of whether the transfusion volume is greater than 300mL of Rh (D) positive blood.

Additionally, The European Medicines Agency Core Summary of Product Characteristics (SPC) for Human Anti-D Immunoglobulin for Intravenous Use states under 'Incompatible transfusions' that a maximum dose of 15,000 IU (3000µg) is sufficient in the case of larger incompatible transfusions independent of whether the transfusion volume is greater than 300mL of Rh(D) positive blood cells.

References:

1. *RHOPHYLAC Product Information, date of TGA approval 01 September 2009*
2. *EMEA Guideline on the Core SPC for Human Anti-D Immunoglobulin for Intravenous Use – Revision 1 (CHMP/BPWP/319619/2005) 1 April 2008*

8.2 What are the major differences between WinRho-SDF and RHOPHYLAC for Rh (D) incompatible transfusion?

Feature	RHOPHYLAC	WinRho-SDF
Viral Inactivation Steps	Solvent detergent & virus filtration	Solvent detergent & virus filtration
Administration	Intravenous or Intramuscular	Intravenous or Intramuscular
Formulation	Ready to use, pre-filled 2mL syringe	Sterile freeze-dried vial and diluent
Presentation	Glass syringe pre-filled with 2mL solution for injection	One vial of sterile freeze dried gamma globulin fraction and one vial of diluent, reconstituted to between 1.25-2.5mL for intravenous injection.
Dose	- 100 IU (20µg) RHOPHYLAC/mL Rh (D) positive red cells - A 1500 IU (300µg) vial will suppress the immunising potential of <15mL of Rh (D) positive red cells. - Maximum dose 15,000 IU (3000µg), independent of whether the transfusion volumes are >300mL of Rh (D) positive blood	- 100 IU (20µg) WinRho-SDF/mL Rh (D) positive red cells - A 600 IU (120µg) vial will suppress the immunising potential of <6mL of Rh(D) positive red cells - Maximum dose 3000 IU q8h IV
Administration (intravenous)	- 2mL (1500 IU) per 15-60 seconds. For multiple vials, 2mL per 60 seconds. - within 72 hours of complication	- 1.25 mL - 2.5mL (480 IU/mL – 240 IU/mL) injected into a suitable vein at a rate of 1500 IU over 5-15 seconds - within 72 hours of complication

References:

1. RHOPHYLAC Product Information, date of TGA approval 01 September 2009

2. WinRho-SDF Product Information, date of most recent amendment 06 May 2010

3. RHOPHYLAC U.S. Package Insert. Date of Initial US Approval 2004. Revised 09/2010

4. EMEA Guideline on the Core SPC for Human Anti-D Immunoglobulin for Intravenous Use – Revision 1 (CHMP/BPWP/319619/2005) 1 April 2008