

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use Rhophylac® safely and effectively. See full prescribing information for Rhophylac®.

Rhophylac®
Rh₀(D) Immune Globulin Intravenous (Human) 1500 IU (300 mcg)
For Intravenous or Intramuscular Injection
Initial US Approval: 2004

INDICATIONS AND USAGE

Rhophylac® is indicated for:

Suppression of rhesus (Rh) isoimmunization (1.1) in:

- Pregnancy and obstetric conditions in non-sensitized, Rh₀(D)-negative women with an Rh-incompatible pregnancy, including:
 - Routine antepartum and postpartum Rh prophylaxis
 - Rh prophylaxis in obstetric complications or invasive procedures
- Incompatible transfusions in Rh₀(D)-negative individuals transfused with blood components containing Rh₀(D)-positive red blood cells (RBCs)

Immune thrombocytopenic purpura (ITP) (1.2)

Raising platelet counts in Rh₀(D)-positive, non-splenectomized adults with chronic ITP

DOSAGE AND ADMINISTRATION

Suppression of Rh Isoimmunization (2.2)

Intravenous or intramuscular administration

- Pregnancy and obstetric conditions
 - Rh-incompatible pregnancy – 1500 IU (300 mcg) at Week 28-30 of gestation and another 1500 IU (300 mcg) within 72 hours of birth of an Rh₀(D)-positive baby
 - Obstetric complications/invasive procedures – 1500 IU (300 mcg) within 72 hours of the at-risk event
 - Excessive fetomaternal hemorrhage – 1500 IU (300 mcg) within 72 hours *plus* 100 IU (20 mcg) per mL fetal RBCs >15 mL (excess transplacental bleeding quantified) *or* another 1500 IU (300 mcg) (excess transplacental bleeding not quantified)
 - Exposure to >15 mL of Rh₀(D)-positive RBCs (in postpartum prophylaxis and obstetric complications/invasive procedures) – Increase the dose based on guidelines for excessive fetomaternal hemorrhage
- Incompatible transfusions – 100 IU (20 mcg) per 2 mL transfused blood or per 1 mL erythrocyte concentrate within 72 hours of exposure

ITP (2.3)

Intravenous administration only

- Recommended dosage – 250 IU (50 mcg) per kg body weight
- Rate of administration – 2 mL per 15 to 60 seconds

DOSAGE FORMS AND STRENGTHS

1500 IU (300 mcg) per 2 mL prefilled syringe (3)

CONTRAINDICATIONS

Anaphylactic or severe systemic reaction to human immune globulin products (4)

WARNINGS AND PRECAUTIONS

Both Indications (5.1)

- Allergic or hypersensitivity reactions may occur; discontinue administration and initiate treatment for shock, if necessary
- Individuals with selective IgA deficiency can develop antibodies to IgA and are at risk of developing severe hypersensitivity and anaphylactic reactions; weigh the benefits of Rhophylac® vs. the potential risks
- Products made from human plasma may contain infectious agents; e.g., viruses and, theoretically, the Creutzfeldt-Jakob disease (CJD) agent

Suppression of Rh Isoimmunization (5.2)

- For postpartum use following an Rh-incompatible pregnancy, Rhophylac® should not be given to the newborn infant

ITP (5.3)

- Intravascular hemolysis has occurred in a clinical study; monitor patients for signs and symptoms and perform confirmatory laboratory tests
- In ITP patients with pre-existing anemia, weigh the benefits of Rhophylac® vs. the potential risk of increasing the severity of the anemia

ADVERSE REACTIONS

Suppression of Rh Isoimmunization

Most common adverse reactions are nausea, dizziness, headache, injection-site pain, and malaise (6.1)

ITP

Most common adverse reactions are chills, pyrexia/increased body temperature, headache, and mild extravascular hemolysis (increased bilirubin, decreased hemoglobin) (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact CSL Behring at 1-800-504-5434 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

Immunoglobulin administration may transiently impair efficacy of live virus vaccines (7.1)

USE IN SPECIFIC POPULATIONS

Suppression of Rh Isoimmunization

- Pediatric patients – Weigh the benefits vs. the potential risks in treating incompatible transfusions (8.4)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 07/2009

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* Sections or subsections omitted from the full prescribing information are not listed.

1 **CSL Behring**

2
3
4 **FULL PRESCRIBING INFORMATION**

5 **Rhopylac®**

6 **Rh₀(D) Immune Globulin Intravenous (Human)**

7
8 For Intravenous or Intramuscular Injection

9 Preservative-free, Latex-free, Ready-to-use Prefilled Syringe

10
11 **1 INDICATIONS AND USAGE**

12
13 **1.1 Suppression of Rh Isoimmunization**

14 Pregnancy and Obstetric Conditions

15 Rhopylac® is indicated for suppression of rhesus (Rh) isoimmunization in non-sensitized
16 Rh₀(D)-negative women with an Rh-incompatible pregnancy, including:

- 17
18 • Routine antepartum and postpartum Rh prophylaxis
- 19
20 • Rh prophylaxis in cases of:
- 21 – Obstetric complications (e.g., miscarriage, abortion, threatened abortion, ectopic
22 pregnancy or hydatidiform mole, transplacental hemorrhage resulting from
23 antepartum hemorrhage)
- 24 – Invasive procedures during pregnancy (e.g., amniocentesis, chorionic biopsy) or
25 obstetric manipulative procedures (e.g., external version, abdominal trauma)

26
27 An Rh-incompatible pregnancy is assumed if the fetus/baby is either Rh₀(D)-positive or
28 Rh₀(D)-unknown or if the father is either Rh₀(D)-positive or Rh₀(D)-unknown.

29
30 Incompatible Transfusions

31 Rhopylac® is indicated for the suppression of Rh isoimmunization in Rh₀(D)-negative
32 individuals transfused with Rh₀(D)-positive red blood cells (RBCs) or blood components
33 containing Rh₀(D)-positive RBCs.

34
35 Treatment can be given without a preceding exchange transfusion when the transfused
36 Rh₀(D)-positive blood represents less than 20% of the total circulating RBCs. If the volume
37 exceeds 20%, an exchange transfusion should be considered prior to administering Rhopylac®.

38
39 **1.2 Immune Thrombocytopenic Purpura (ITP)**

40 Rhopylac® is indicated in Rh₀(D)-positive, non-splenectomized adult patients with
41 chronic ITP to raise platelet counts.

44 **2 DOSAGE AND ADMINISTRATION**

45

46 As with all blood products, patients should be observed for at least 20 minutes following
47 administration of Rhophylac®.

48

49 **2.1 Preparation and Handling**

50 Bring Rhophylac® to room temperature before use.

51

52 Rhophylac® is a clear or slightly opalescent, colorless to pale yellow solution.
53 Rhophylac® should be inspected visually for particulate matter and discoloration prior to
54 administration. Do not use if the solution is cloudy or contains particulates. Do not use
55 solution that has been frozen.

56

57 Rhophylac® is for single use only. Dispose of any unused product or waste material in
58 accordance with local requirements.

59

60 **2.2 Suppression of Rh Isoimmunization**

61 Rhophylac® should be administered by intravenous or intramuscular injection. If large
62 doses (greater than 5 mL) are required and intramuscular injection is chosen, it is advisable to
63 administer Rhophylac® in divided doses at different sites.

64

65 Table 1 provides dosing guidelines based on the condition being treated.

66

67

67 **Table 1: Dosing Guidelines for Suppression of Rh Isoimmunization**
68

Indication	Timing of Administration	Dose* (Administer by Intravenous or Intramuscular Injection)
Rh-incompatible pregnancy		
Routine antepartum prophylaxis	At Week 28-30 of gestation	1500 IU (300 mcg)
Postpartum prophylaxis (required only if the newborn is Rh ₀ (D)-positive)	Within 72 hours of birth	1500 IU (300 mcg) [†]
Obstetric complications (e.g., miscarriage, abortion, threatened abortion, ectopic pregnancy or hydatidiform mole, transplacental hemorrhage resulting from antepartum hemorrhage)	Within 72 hours of complication	1500 IU (300 mcg) [†]
Invasive procedures during pregnancy (e.g., amniocentesis, chorionic biopsy) or obstetric manipulative procedures (e.g., external version, abdominal trauma)	Within 72 hours of procedure	1500 IU (300 mcg) [†]
Excessive fetomaternal hemorrhage (>15 mL)	Within 72 hours of complication	1500 IU (300 mcg) <i>plus</i> : <ul style="list-style-type: none"> • 100 IU (20 mcg) per mL fetal RBCs in excess of 15 mL if excess transplacental bleeding is quantified <p style="text-align: center;"><i>or</i></p> <ul style="list-style-type: none"> • An additional 1500 IU (300 mcg) dose if excess transplacental bleeding cannot be quantified
Incompatible transfusions	Within 72 hours of exposure	100 IU (20 mcg) per 2 mL transfused blood or per 1 mL erythrocyte concentrate

69 IU, international units; mcg, micrograms.

70 * A 1500 IU (300 mcg) dose of Rhophylac® will suppress the immunizing potential of ≥15 mL of Rh₀(D)-positive RBCs.¹

71 † The dose of Rhophylac® must be increased if the patient is exposed to >15 mL of Rh₀(D)-positive RBCs; in this case, follow
72 the dosing guidelines for excessive fetomaternal hemorrhage.

73

74

74 **2.3 ITP**

75 For treatment of ITP, Rhophylac® **must be administered by the intravenous route.**

76

77 A 250 IU (50 mcg) per kg body weight dose of Rhophylac® is recommended for patients
78 with ITP. The following formula can be used to calculate the amount of Rhophylac® to
79 administer:

80

81 $\text{Dose (IU)} \times \text{body weight (kg)} = \text{Total IU} / 1500 \text{ IU per syringe} = \# \text{ of syringes}$

82

83 Rhophylac® should be administered at a rate of 2 mL per 15 to 60 seconds.

84

85

86 **3 DOSAGE FORMS AND STRENGTHS**

87

88 1500 IU (300 mcg) per 2 mL prefilled syringe

89

90

91 **4 CONTRAINDICATIONS**

92

93 Individuals known to have had an anaphylactic or severe systemic reaction to the
94 administration of human immune globulin products should not receive Rh₀(D) immune
95 globulin.

96

97

98 **5 WARNINGS AND PRECAUTIONS**

99

100 **5.1 Both Indications**

101 Allergic Reactions

102 Allergic reactions may occur. If symptoms of allergic or early signs of hypersensitivity
103 reactions (including generalized urticaria, tightness of the chest, wheezing, hypotension, and
104 anaphylaxis) occur, immediately discontinue administration. The treatment required depends
105 on the nature and severity of the side effect. If necessary, the current medical standards for
106 shock treatment should be observed (*see Patient Counseling Information [17.1]*).

107

108 Selective IgA Deficiency

109 Individuals with selective IgA deficiency can develop antibodies to IgA and anaphylactic
110 reactions (including anaphylaxis and shock) after administration of blood components
111 containing IgA. Although the concentration of IgA was found to be below the detection limit of
112 5 mcg/mL, Rhophylac® may contain trace amounts of IgA (*see Description [11]*).

113

114 Those with known antibodies to IgA may have a greater risk of developing potentially
115 severe hypersensitivity and anaphylactic reactions. Therefore, the physician must weigh the
116 expected benefits of treatment with Rhophylac® against the potential risks.

117

Interference With Laboratory Tests

The administration of Rh₀(D) immune globulin may affect the results of blood typing, the antibody screening test, and the direct antiglobulin (Coombs') test. Antepartum administration of Rh₀(D) immune globulin to the mother can also affect these tests in the newborn infant.

Rhophylac® can contain antibodies to other Rh antigens (e.g., anti-C antibodies), which might be detected by sensitive serological tests following administration.

Transmissible Infectious Agents

Rhophylac® is made from human plasma. Products made from human plasma may contain infectious agents, e.g., viruses and, theoretically, the Creutzfeldt-Jakob disease (CJD) agent, that can cause disease. The risk that such products will transmit an infectious agent has been reduced by screening plasma donors for prior exposure to certain viruses, by testing for the presence of certain current virus infections, and by inactivating and/or removing certain viruses during manufacturing through solvent/detergent treatment and virus filtration. The solvent/detergent treatment step is effective in inactivating enveloped viruses such as hepatitis B virus (HBV), hepatitis C virus (HCV), and human immunodeficiency virus (HIV). The virus filtration step is effective in removing both enveloped and non-enveloped viruses (*see Description [11], Patient Counseling Information [17.1]*).

Despite these measures, such products can still potentially transmit disease. There is also the possibility that unknown infectious agents may be present in such products. All infections thought by a physician possibly to have been transmitted by this product should be reported by the physician or other healthcare provider to CSL Behring at 1-800-504-5434. The physician should discuss the risks and benefits of this product with the patient.

5.2 Suppression of Rh Isoimmunization

Postpartum Use Following an Rh-incompatible Pregnancy

Rhophylac® should not be given to the newborn infant (*see Pediatric Use [8.4] for pediatric use in incompatible transfusions and in ITP*).

5.3 ITP

Intravascular Hemolysis

Intravascular hemolysis has occurred in a clinical study with Rhophylac®. All cases resolved completely. However, as reported in the literature, some patients treated with Rh₀(D) immune globulin (anti-D) developed clinically compromising anemia, acute renal insufficiency, and, very rarely, disseminated intravascular coagulation (DIC) and death.²

Following administration of Rhophylac®, patients should be monitored for signs and/or symptoms of intravascular hemolysis and its complications including clinically compromising anemia, acute renal insufficiency, and DIC. Patients experiencing intravascular hemolysis may present with back pain, shaking chills, fever, and, most consistently, hemoglobinuria (*see Patient Counseling Information [17.3]*).

ITP patients presenting with signs and/or symptoms of intravascular hemolysis and its complications after Rh₀(D) immune globulin administration should have confirmatory

164 laboratory tests. DIC may be difficult to detect in the ITP population; the diagnosis is
165 dependent mainly on laboratory testing.

166

167 If patients who develop hemolysis with clinically compromising anemia after receiving
168 Rhophylac® are to be transfused, Rh₀(D)-negative packed RBCs should be used to avoid
169 exacerbating ongoing hemolysis.

170

171 Pre-existing Anemia

172 The safety of Rhophylac® in the treatment of ITP has not been established in patients with
173 pre-existing anemia. The physician must weigh the benefits of Rhophylac® against the potential
174 risk of increasing the severity of the anemia.

175

176

177 **6 ADVERSE REACTIONS**

178

179 The most serious adverse reactions in patients receiving Rh₀(D) immune globulin have
180 been observed in the treatment of ITP. These reactions include intravascular hemolysis,
181 clinically compromising anemia, acute renal insufficiency, and, very rarely, DIC and death (*see*
182 *Warnings and Precautions [5.3]*).

183

184 The most common adverse reactions observed in the use of Rhophylac® for suppression of
185 Rh isoimmunization are nausea, dizziness, headache, injection-site pain, and malaise.

186

187 The most common adverse reactions observed in the treatment of ITP are chills,
188 pyrexia/increased body temperature, and headache. Mild extravascular hemolysis (manifested
189 by an increase in bilirubin and a decrease in hemoglobin) was also observed.

190

191 **6.1 Clinical Studies Experience**

192 *Because clinical studies are conducted under different protocols and widely varying*
193 *conditions, adverse reaction rates observed cannot be directly compared to rates in other*
194 *clinical trials and may not reflect the rates observed in practice.*

195

196 Suppression of Rh Isoimmunization

197 In two clinical studies, 447 Rh₀(D)-negative pregnant women received either an
198 intravenous or intramuscular injection of Rhophylac® 1500 IU (300 mcg) at Week 28 of
199 gestation. A second 1500 IU (300 mcg) dose was administered to 267 (9 in Study 1 and 258 in
200 Study 2) of these women within 72 hours of the birth of an Rh₀(D)-positive baby. In addition,
201 30 women in Study 2 received at least one extra antepartum 1500 IU (300 mcg) dose due to
202 obstetric complications (*see Clinical Studies [14.1]*).

203

204 The most common adverse reactions were nausea (0.7%), dizziness (0.5%), headache
205 (0.5%), injection-site pain (0.5%), and malaise (0.5%). A laboratory finding of a transient
206 positive anti-C antibody test was observed in 0.9% of subjects. All adverse reactions were mild
207 to moderate in intensity.

208

209 ITP

210 In a clinical study, 98 Rh₀(D)-positive adult subjects with chronic ITP received an
 211 intravenous dose of Rhophylac® 250 IU (50 mcg) per kg body weight (*see Clinical Studies*
 212 *[14.2]*). Premedication to alleviate infusion-related side effects was not used except in a single
 213 subject who received acetaminophen and diphenhydramine.

214
 215 Adverse reactions were mild to moderate in intensity with the exception of one case of
 216 severe headache. Eighty-four (85.7%) subjects experienced 392 treatment-emergent adverse
 217 events (TEAEs). Sixty-nine (70.4%) subjects had 186 drug-related TEAEs (defined as TEAEs
 218 with a probable, possible, definite, or unknown relationship to the study drug). Within 24 hours
 219 of dosing, 73 (74.5%) subjects experienced 183 TEAEs, and 66 (67%) subjects experienced 156
 220 drug-related TEAEs.

221
 222 Mild extravascular hemolysis, manifested as an increase in bilirubin, a decrease in
 223 hemoglobin, or a decrease in haptoglobin, was observed, as expected when an anti-D product is
 224 given to an Rh-positive individual. An increase in blood bilirubin was seen in 21% of subjects.
 225 The median decrease in hemoglobin was greatest (0.8 g/dL) at Day 6 and Day 8 following
 226 administration of Rhophylac®.

227
 228 Table 2 shows the most common TEAEs observed in the clinical study.

229
 230 **Table 2: Most Common Treatment-Emergent Adverse Events (TEAEs) in Subjects With**
 231 **ITP**

TEAE	Number of Subjects (%) With a TEAE n=98	Number of Subjects (%) With a Drug-Related TEAE* n=98
Chills	34 (34.7%)	34 (34.7%)
Pyrexia/ Increased body temperature	32 (32.6%)	30 (30.6%)
Increased blood bilirubin	21 (21.4%)	21 (21.4%)
Headache	14 (14.3%)	11 (11.2%)

232
 233 * Defined as TEAEs with a possible, probable, definite, or unknown relationship to the study drug.

234
 235 Serious adverse events (SAEs) were reported in 10 (10.2%) subjects. SAEs considered to
 236 be drug-related were intravascular hemolytic reaction (hypotension, nausea, chills and
 237 headache, and a decrease in haptoglobin and hemoglobin) in two subjects; headache, dizziness,
 238 nausea, pallor, shivering, and weakness requiring hospitalization in one subject; and an increase
 239 in blood pressure and severe headache in one subject. All four subjects recovered completely.

240 **6.2 Postmarketing Experience**

241
 242 *Because postmarketing reporting of adverse reactions is voluntary and from a population*
 243 *of uncertain size, it is not always possible to reliably estimate their frequency or establish a*
 244 *causal relationship to product exposure. Evaluation and interpretation of these postmarketing*

245 *reactions is confounded by underlying diagnosis, concomitant medications, pre-existing*
246 *conditions, and inherent limitations of passive surveillance.*

247

248 Suppression of Rh Isoimmunization

249 The following adverse reactions have been identified during postapproval use of
250 Rhophylac® for suppression of Rh isoimmunization: hypersensitivity reactions, including rare
251 cases of anaphylactic shock or anaphylactoid reactions, headache, dizziness, vertigo,
252 hypotension, tachycardia, dyspnea, nausea, vomiting, rash, erythema, pruritus, chills, pyrexia,
253 malaise, and, rarely, diarrhea and back pain. Transient injection-site irritation and pain have
254 been observed following intramuscular administration.

255

256 ITP

257 Transient hemoglobinuria has been reported in a patient being treated with Rhophylac® for
258 ITP.

259

260

261 **7 DRUG INTERACTIONS**

262

263 **7.1 Live Virus Vaccines**

264 Immunoglobulin administration may transiently impair the efficacy of live attenuated
265 virus vaccines such as measles, mumps, rubella, and varicella. The immunizing physician
266 should be informed of recent therapy with Rhophylac® so that appropriate measures can be
267 taken (*see Patient Counseling Information [17.1]*).

268

269

270 **8 USE IN SPECIFIC POPULATIONS**

271

272 **8.1 Pregnancy**

273 Pregnancy Category C. Animal reproduction studies have not been conducted with
274 Rhophylac®.

275

276 Suppression of Rh Isoimmunization

277 The available evidence suggests that Rhophylac® does not harm the fetus or affect future
278 pregnancies or reproduction capacity when given to pregnant Rh₀(D)-negative women for
279 suppression of Rh isoimmunization.

280

281 ITP

282 Rhophylac® has not been evaluated in pregnant women with ITP.

283

284 **8.3 Nursing Mothers**

285 Suppression of Rh Isoimmunization

286 Rhophylac® is used in nursing mothers for the suppression of Rh isoimmunization. No
287 undesirable effects on a nursing infant are expected during breastfeeding.

288

289 ITP

290 Rhophylac® has not been evaluated in nursing mothers with ITP.

291
292 **8.4 Pediatric Use**
293 Suppression of Rh Isoimmunization in Incompatible Transfusions
294 The safety and effectiveness of Rhophylac® have not been established in pediatric subjects
295 being treated for an incompatible transfusion. The physician should weigh the potential risks
296 against the benefits of Rhophylac®, particularly in girls whose later pregnancies may be affected
297 if Rh isoimmunization occurs.

298
299 ITP
300 Studies have demonstrated the safe and effective use of Rh₀(D) Immune Globulin in
301 children with ITP.³⁻⁶

302
303 **8.5 Geriatric Use**
304 Suppression of Rh Isoimmunization in Incompatible Transfusions
305 Rhophylac® has not been evaluated for treating incompatible transfusions in subjects 65
306 years of age and older.

307
308 ITP
309 Of the 98 subjects evaluated in the clinical study of Rhophylac® for treatment of ITP (*see*
310 *Clinical Studies [14.2]*), 19% were 65 years of age and older. No overall differences in
311 effectiveness or safety were observed between these subjects and younger subjects.

312
313
314 **10 OVERDOSAGE**

315
316 There are no reports of known overdoses in patients being treated for suppression of Rh
317 isoimmunization or ITP. Patients with incompatible transfusion or ITP who receive an
318 overdose of Rh₀(D) immune globulin should be monitored because of the risk of hemolysis.

319
320
321 **11 DESCRIPTION**

322
323 Rhophylac® is a sterile Rh₀(D) Immune Globulin Intravenous (Human) solution in a
324 ready-to-use prefilled syringe for intravenous or intramuscular injection. One syringe contains
325 at least 1500 IU (300 mcg) of IgG antibodies to Rh₀(D) in a 2 mL solution, sufficient to
326 suppress the immune response to at least 15 mL of Rh-positive RBCs.¹ The product potency is
327 expressed in IUs by comparison to the World Health Organization (WHO) standard, which is
328 also the US and the European Pharmacopoeia standard.

329
330 Plasma is obtained from healthy Rh₀(D)-negative donors who have been immunized with
331 Rh₀(D)-positive RBCs. The donors are screened carefully to reduce the risk of receiving
332 donations containing blood-borne pathogens. Each plasma donation used in the manufacture of
333 Rhophylac® is tested for the presence of HBV surface antigen (HBsAg), HIV-1/2, and HCV
334 antibodies. In addition, plasma used in the manufacture of Rhophylac® is tested by FDA-
335 licensed Nucleic Acid Testing (NAT) for HIV and HCV and found to be negative. An
336 investigational NAT for HBV is also performed on all source plasma used and found to be

337 negative; however, the significance of a negative result has not been established. The source
338 plasma is also tested by NAT for hepatitis A virus (HAV) and B19 virus (B19V).
339

340 Rhophylac® is produced by an ion-exchange chromatography isolation procedure⁷, using
341 pooled plasma obtained by plasmapheresis of immunized Rh₀(D)-negative US donors. The
342 manufacturing process includes a solvent/detergent treatment step (using tri-n-butyl phosphate
343 and Triton™ X-100) that is effective in inactivating enveloped viruses such as HIV, HCV, and
344 HBV.^{8,9} Rhophylac® is filtered using a Planova® 15 nanometer (nm) virus filter that has been
345 validated to be effective in removing both enveloped and non-enveloped viruses. Table 3
346 presents viral clearance and inactivation data from validation studies, expressed as the mean
347 log₁₀ reduction factor.
348

349 **Table 3: Virus Inactivation and Removal in Rhophylac®**
350

Virus	HIV	PRV	BVDV	MVM
Genome	RNA	DNA	RNA	DNA
Envelope	Yes	Yes	Yes	No
Size	80-100 nm	120-200 nm	40-70 nm	18-24 nm
Solvent/detergent treatment	≥6.0	≥5.6	≥5.4	Not tested
Chromatographic process steps	4.5	≥3.9	1.6	≥2.6
Virus filtration	≥6.3	≥5.6	≥5.5	3.4
Overall reduction (log ₁₀ units)	≥16.8	≥15.1	≥12.5	≥6.0

351 HIV, a model for HIV-1 and HIV-2; PRV, pseudorabies virus, a model for large, enveloped DNA viruses
352 (e.g., herpes virus); BVDV, bovine viral diarrhea virus, a model for HCV; MVM, minute virus of mice, a
353 model for B19V and other small, non-enveloped DNA viruses.
354

355 Rhophylac® contains a maximum of 30 mg/mL of human plasma proteins, 10 mg/mL of
356 which is human albumin added as a stabilizer. Prior to the addition of the stabilizer,
357 Rhophylac® has a purity greater than 95% IgG. Rhophylac® contains less than 5 mcg/mL of
358 IgA, which is the limit of detection. Additional excipients are approximately 20 mg/mL of
359 glycine and up to 0.25 M of sodium chloride. Rhophylac® contains no preservative. Human
360 albumin is manufactured from pooled plasma of US donors by cold ethanol fractionation,
361 followed by pasteurization.
362

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364 **12 CLINICAL PHARMACOLOGY**
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366 **12.1 Mechanism of Action**

367 Suppression of Rh Isoimmunization

368 The mechanism by which Rh₀(D) immune globulin suppresses immunization to Rh₀(D)-
369 positive RBCs is not completely known.
370

371 In a clinical study of Rh₀(D)-negative healthy male volunteers, both the intravenous and
372 intramuscular administration of a 1500 IU (300 mcg) dose of Rhophylac® 24 hours after
373 injection of 15 mL of Rh₀(D)-positive RBCs resulted in an effective clearance of Rh₀(D)-
374 positive RBCs. On average, 99% of injected RBCs were cleared within 12 hours following
375 intravenous administration and within 144 hours following intramuscular administration.

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ITP

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12.3 Pharmacokinetics

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Suppression of Rh Isoimmunization

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Following intravenous administration, peak serum levels of Rh₀(D) immune globulin ranged from 62 to 84 ng/mL after 1 day (i.e., the time the first blood sample was taken following the antepartum dose). Mean systemic clearance was 0.20 ± 0.03 mL/min, and half-life was 16 ± 4 days.

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Following intramuscular administration, peak serum levels ranged from 7 to 46 ng/mL and were achieved between 2 and 7 days. Mean apparent clearance was 0.29 ± 0.12 mL/min, and half-life was 18 ± 5 days. The absolute bioavailability of Rhophylac® was 69%.

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401

Regardless of the route of administration, Rh₀(D) immune globulin titers were detected in all women up to at least 9 weeks following administration of Rhophylac®.

402

ITP

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Pharmacokinetic studies with Rhophylac® were not performed in Rh₀(D)-positive subjects with ITP. Rh₀(D) immune globulin binds rapidly to Rh₀(D)-positive erythrocytes.¹²

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14 CLINICAL STUDIES

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409

14.1 Suppression of Rh Isoimmunization

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In two clinical studies, 447 Rh₀(D)-negative pregnant women received a 1500 IU (300 mcg) dose of Rhophylac® during Week 28 of gestation. The women who gave birth to an Rh₀(D)-positive baby received a second 1500 IU (300 mcg) dose within 72 hours of birth.

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419

- Study 1 – Eight of the women who participated in the pharmacokinetic study (*see Clinical Pharmacology [12.3]*) gave birth to an Rh₀(D)-positive baby and received the postpartum dose of 1500 IU (300 mcg) of Rhophylac®.¹¹ Antibody tests performed 6 to 8 months later were negative for all women. This suggests that no Rh₀(D) immunization occurred.

420

421

- Study 2 – In an open-label, single-arm clinical study at 22 centers in the US and United Kingdom, 432 pregnant women received the antepartum dose of 1500 IU (300

422 mcg) of Rhophylac® either as an intravenous or intramuscular injection (two
423 randomized groups of 216 women each).¹³ Subjects received an additional 1500 IU
424 (300 mcg) dose if an obstetric complication occurred between the routine antepartum
425 dose and birth or if extensive fetomaternal hemorrhage was measured after birth. Of
426 the 270 women who gave birth to an Rh₀(D)-positive baby, 248 women were
427 evaluated for Rh₀(D) immunization 6 to 11.5 months postpartum. None of these
428 women developed antibodies against the Rh₀(D) antigen.

429

430 **14.2 ITP**

431 In an open-label, single-arm, multicenter study, 98 Rh₀(D)-positive adult subjects with
432 chronic ITP and a platelet count of $30 \times 10^9/L$ or less were treated with Rhophylac®. Subjects
433 received a single intravenous dose of 250 IU (50 mcg) per kg body weight.

434

435 The primary efficacy endpoint was the response rate defined as achieving a platelet count
436 of $\geq 30 \times 10^9/L$ as well as an increase of $>20 \times 10^9/L$ within 15 days after treatment with
437 Rhophylac®. Secondary efficacy endpoints included the response rate defined as an increase in
438 platelet counts to $\geq 50 \times 10^9/L$ within 15 days after treatment and, in subjects who had bleeding
439 at baseline, the regression of hemorrhage defined as any decrease from baseline in the severity
440 of overall bleeding status.

441

442 Table 4 presents the primary response rates for the intent-to-treat (ITT) and per-protocol
443 (PP) populations.

444

445 **Table 4: Primary Response Rates (ITT and PP Populations)**

446

Analysis Population	No. Subjects	No. Responders	Primary Response Rate at Day 15	
			% Responders	95% Confidence Interval (CI)
ITT	98	65	66.3%	56.5%, 74.9%
PP	92	62	67.4%	57.3%, 76.1%

447

448 The primary efficacy response rate (ITT population) demonstrated a clinically relevant
449 response to treatment, i.e., the lower bound of the 95% CI was greater than the predefined
450 response rate of 50%. The median time to platelet response was 3 days, and the median
451 duration of platelet response was 22 days.

452

453 Table 5 presents the response rates by baseline platelet count for subjects in the ITT
454 population.

455

456

456 **Table 5: Response Rates By Baseline Platelet Count (ITT Population)**
457

Baseline Platelet count (x 10 ⁹ /L)	Total No. Subjects	Response Rates at Day 15	
		No. (%) Subjects Achieving a Platelet Count of ≥30 x 10 ⁹ /L and an Increase of >20 x 10 ⁹ /L	No. (%) Subjects With an Increase in Platelet Counts to ≥50 x 10 ⁹ /L
≤10	38	15 (39.5)	10 (26.3)
>10 to 20	28	22 (78.6)	17 (60.7)
>20 to 30	27	24 (88.9)	22 (81.5)
>30*	5	4 (80.0)	5 (100.0)
Overall (all subjects)	98	65 (66.3)	54 (55.1)

* Reflects subjects with a platelet count of ≤30 × 10⁹/L at screening but >30 × 10⁹/L immediately before treatment.

458
459 During the study, an overall regression of hemorrhage was seen in 44 (88%, 95% CI: 76%
460 to 94%) of the 50 subjects with bleeding at baseline. The percentage of subjects showing a
461 regression of hemorrhage increased from 20% at Day 2 to 64% at Day 15. There was no
462 evidence of an association between the overall hemorrhage regression rate and baseline platelet
463 count.

464
465 Approximately half of the 98 subjects in the ITT population had evidence of bleeding at
466 baseline. Post-baseline, the percentage of subjects without bleeding increased to a maximum of
467 70.4% at Day 8.

468
469

470 15 REFERENCES

- 471
- 472 1. Pollack W, Ascari WQ, Kochesky RJ, O'Connor RR, Ho TY, Tripodi D. Studies on
473 Rh prophylaxis. 1. relationship between doses of anti-Rh and size of antigenic
474 stimulus. *Transfusion*. 1971;11:333-339.
 - 475 2. Gaines AR. Disseminated intravascular coagulation associated with acute
476 hemoglobinemia or hemoglobinuria following Rh₀(D) immune globulin intravenous
477 administration for immune thrombocytopenic purpura. *Blood*. 2005;106:1532-1537.
 - 478 3. Tarantino MD, Young G, Bertolone SJ, et al; Acute ITP Study Group. Single dose of
479 anti-D immune globulin at 75 μg/kg is as effective as intravenous immune globulin at
480 rapidly raising the platelet count in newly diagnosed immune thrombocytopenic
481 purpura in children. *J Pediatr*. 2006;148:489-94.
 - 482 4. Scaradavou A, Woo B, Woloski BM, et al. Intravenous anti-D treatment of immune
483 thrombocytopenic purpura: experience in 272 patients. *Blood*. 1997 15;89:2689-2700.
 - 484 5. Andrew M, Blanchette VS, Adams M, et al. A multicenter study of the treatment of
485 childhood chronic idiopathic thrombocytopenic purpura with anti-D. *J Pediatr*.
486 1992;120:522-527.

- 487 6. Blanchette V, Imbach P, Andrew M, et al. Randomised trial of intravenous
488 immunoglobulin G, intravenous anti-D, and oral prednisone in childhood acute
489 immune thrombocytopenic purpura. *Lancet*. 1994;344:703-707.
- 490 7. Stucki M, Moudry R, Kempf C, Omar A, Schlegel A, Lerch PG. Characterisation of a
491 chromatographically produced anti-D immunoglobulin product. *J Chromatogr B*.
492 1997;700:241-248.
- 493 8. Horowitz B, Chin S, Prince AM, Brotman B, Pascual D, Williams B. Preparation and
494 characterization of S/D-FFP, a virus sterilized “fresh frozen plasma”. *J Thromb*
495 *Haemost*. 1991;65:1163.
- 496 9. Horowitz B, Bonomo R, Prince AM, Chin S, Brotman B, Shulman RW.
497 Solvent/detergent-treated plasma: a virus-inactivated substitute for fresh frozen
498 plasma. *Blood*. 1992;79:826-831.
- 499 10. Lazarus AH, Crow AR. Mechanism of action of IVIG and anti-D in ITP. *Transfus*
500 *Apher Sci*. 2003;28:249-255.
- 501 11. Bichler J, Schöndorfer G, Pabst G, Andresen I. Pharmacokinetics of anti-D IgG in
502 pregnant RhD-negative women. *BJOG*. 2003;110:39-45.
- 503 12. Ware RE, Zimmerman SA. Anti-D: mechanisms of action. *Semin Hematol*.
504 1998;35:14-22.
- 505 13. MacKenzie IZ, Bichler J, Mason GC, et al. Efficacy and safety of a new,
506 chromatographically purified rhesus (D) immunoglobulin. *Eur J Obstetr Gynecol*
507 *Reprod Biol*. 2004;117:154-161.

510 16 HOW SUPPLIED/STORAGE AND HANDLING

511
512 Rhophylac® 1500 IU (300 mcg) is supplied in packages of one or 10 latex-free, ready-to-
513 use, prefilled syringes, each containing 2 mL of preservative-free liquid. Each syringe is
514 accompanied by a SafetyGlide™ needle for intravenous or intramuscular use.

516 NDC Number	516 Product Description
517 44206-300-01	517 1 prefilled 2 mL syringe
518 44206-300-10	518 10 prefilled 2 mL syringes

519
520 Store at 2–8°C (36–46°F). If stored at this temperature, Rhophylac® has a shelf life of 36
521 months from the date of manufacture, as indicated by the expiration date printed on the outer
522 carton and syringe label. Do not freeze. Keep Rhophylac® in its original carton to protect it
523 from light.

526 **17 PATIENT COUNSELING INFORMATION**

527

528 **17.1 Both Indications**529 Allergic Reactions

530 Inform patients of the early signs of allergic or hypersensitivity reactions to Rhophylac®
531 including hives, chest tightness, wheezing, hypotension, and anaphylaxis (*see Warnings and*
532 *Precautions [5.1]*) and advise them to notify their physician if they experience any of these
533 symptoms.

534

535 Transmissible Infectious Agents

536 Inform patients that Rhophylac® is made from human plasma (part of the blood) and may
537 contain infectious agents that can cause disease (e.g., viruses and, theoretically, the CJD agent).
538 Explain that the risk that Rhophylac® may transmit an infectious agent has been reduced by
539 screening the plasma donors, by testing the donated plasma for certain virus infections, and by
540 inactivating and/or removing certain viruses during manufacturing (*see Warnings and*
541 *Precautions [5.1]*).

542

543 Live Virus Vaccines

544 Inform patients that administration of immunoglobulin may temporarily impair the
545 effectiveness of live virus vaccines (e.g., measles, mumps, rubella, and varicella) and to notify
546 their immunizing physician of recent therapy with Rhophylac® (*see Drug Interactions [7.1]*).

547

548 **17.2 Suppression of Rh Isoimmunization**549 Standard Dosing for Rh Isoimmunization

550 Inform patients receiving the antepartum dose of Rhophylac® for suppression of Rh
551 isoimmunization that they will need a second dose within 72 hours of birth if the baby's blood
552 type is Rh-positive (*see Dosage and Administration for Suppression of Rh Isoimmunization*
553 *[2.2]*).

554

555 **17.3 ITP**556 Intravascular Hemolysis

557 Instruct patients being treated with Rhophylac® for ITP **to immediately report** symptoms
558 of intravascular hemolysis, including back pain, shaking chills, fever, discolored urine,
559 decreased urine output, sudden weight gain, edema, and/or shortness of breath (*see Warnings*
560 *and Precautions [5.3]*).

561

562

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576

577 Part Number: 6402/103