SUMMARY OF BASIS FOR APPROVAL

STN:	**BL 125070/0**
Licensed Name:	**Rh_o(D) Immune Globulin Intravenous (Human)**
Applicant /Manufacturer:	**ZLB Bioplasma AG** **Wankdorfstrasse10** **CH-3000 Bern 22** **Switzerland**
Proprietary Name:	**Rhophylac®**

I. Indication for Use

Rhophylac®, a Rh_o(D) Immune Globulin Intravenous (Human) product, is recommended for the routine antepartum and postpartum suppression of Rhesus immunization in non-sensitized Rh_o(D)-negative (D-negative) women; for Rhesus prophylaxis in case of obstetric complications, e.g., miscarriage, abortion, threatened abortion, ectopic pregnancy or hydatidiform mole, transplacental hemorrhage resulting from antepartum hemorrhage; and for Rhesus prophylaxis in case of invasive procedures during pregnancy, e.g., amniocentesis, chorionic biopsy or obstetric manipulative procedures, e.g., external version, or abdominal trauma. In addition, Rhophylac® is recommended for the suppression of Rhesus immunization in Rh_o(D)-negative individuals transfused with Rh_o(D)-positive red blood cells (RBCs) or blood components containing Rh_o(D)-positive RBCs.

Pregnancy and Obstetrical Conditions

Rhophylac® is recommended:

1. For the suppression of Rh isoimmunization in non-sensitized Rh_o(D)-negative (D-negative) women.

The criteria for an Rh-incompatible pregnancy requiring administration of Rhophylac® at 28 weeks gestation and within 72 hours after delivery are:

- The mother must be Rh_o(D) negative;
- The mother is carrying a child whose father is either Rh_o(D)-positive or Rh_o(D) unknown; and
- The baby is either Rh_o(D)-positive or Rh_o(D) unknown, and the mother must not be previously sensitized to the Rh_o(D) factor.

2. For Rhesus prophylaxis in case of obstetric complications, e.g., miscarriage, abortion, threatened abortion, ectopic pregnancy or hydatidiform mole, transplacental hemorrhage resulting from antepartum hemorrhage.

3. For Rhesus prophylaxis in case of invasive procedures during pregnancy, e.g., amniocentesis, chorionic biopsy or obstetric manipulative procedures, e.g., external version, or abdominal trauma.

Incompatible Transfusion

Rhophylac® is recommended for the suppression of Rhesus immunization in Rh_o(D)-negative individuals transfused with Rh_o(D)-positive RBCs or blood components containing Rh_o(D)-positive RBCs. Treatment should be initiated within 72 hours of exposure. Treatment should be given (without preceding exchange transfusion) only if the transfused Rh_o(D)-positive blood represents less than 20% of the total circulating red cells. A 1500 IU (300 µg) dose will suppress the immunizing potential of approximately 15 mL of Rh_o(D)-positive RBCs.

II. Dosage and Route of Administration

Rhophylac® is a sterile Rh_o(D) Immune Globulin Intravenous (Human) solution in a prefilled, ready-for-use syringe for either intravenous (IV) or intramuscular (IM) injection. One syringe contains at least 1500 IU (300 µg) of IgG antibodies to Rh_o(D) in a 2 mL solution, sufficient to suppress the immune response to at least 15 mL of Rh_o(D)-positive RBCs. The product potency is expressed in international units by comparison to the World Health Organization (WHO) standard, which is the US and the European Pharmacopoeia standard.

Pregnancy and Obstetrical Conditions

A dose of 1500 IU (300 µg) is recommended for:

- The routine antepartum (at 28 to 30 weeks of gestation) and postpartum (up to 72 hours) prevention of Rh_o(D) immunization in Rh_o(D)-negative women;

- For Rhesus prophylaxis in case of obstetric complications, e.g., miscarriage, abortion, threatened abortion, ectopic pregnancy or hydatidiform mole, transplacental hemorrhage resulting from antepartum hemorrhage;

- For Rhesus prophylaxis in case of invasive procedures during pregnancy, e.g., amniocentesis, chorionic biopsy or obstetric manipulative procedures, external version, or abdominal trauma.

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 [100 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_o(D)-positive red blood cells.

Incompatible Transfusion

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

Route of Administration

Rhophylac® should be brought to room or body temperature before use. Rhophylac® should be administered by slow IV or by IM injection. If large doses (> 5 mL) are required and IM 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

III. Manufacturing and Controls

Production

Pooling

The product is manufactured from pooled source plasma selected for high titers of antibodies to Rhesus D-positive erythrocytes. The plasma units are tested and found non-reactive for HBsAg, anti-hepatitis C virus (HCV), and anti-human immunodeficiency viruses (HIV)-1/2, and with limited alanine aminotransferase (ALT)-activity. In addition, plasma was tested by FDA licensed Nucleic Acid Testing (NAT) for HIV and HCV and by an investigational NAT for HBV. Plasma has also been tested by NAT for hepatitis A virus (HAV) and parvovirus B19 on pooled samples.

Separation of cryoprecipitate

After thawing, the plasma pool is centrifuged and the cryoprecipitate is discarded.

Solvent/detergent-treatment (S/D-treatment)

The cryo-depleted plasma pool is filtered. Then virus inactivation takes place by means of a S/D-treatment with 1% Triton X-100 and 1% tri-n-butylphosphate (TnBP) for a total of ------- at -----. The S/D-treated solution is then allowed to stand for ----------. It separates into two phases; the upper egg yolk-like phase is discarded.

---------- Chromatography 1

The lower plasma phase is inline-diluted, filtered, and then passed through an ion-exchange column. The column is subsequently washed and the IgG-fraction containing anti-D is eluted.

DEAE-Sephadex® ----treatment

The eluate obtained in the previous step is diluted, pH-adjusted, and adsorbed in batch method with washed and equilibrated DEAE-Sephadex® ---. The unbound anti-D IgG fraction is filtered through a polypropylene mesh, and the gel washed with sodium phosphate buffer. Filtrate and wash solution are mixed and the pH is adjusted.

Alhydrogel® treatment

The DEAE-filtrate is incubated with Alhydrogel®, which is then removed by filtration through a polypropylene mesh with a filter aid.

---------- chromatography 2

The Alhydrogel®-filtrate is concentrated on a second cation-exchange column; the bound IgG-fraction containing anti-D is then eluted.

Nanofiltration

The eluate from the previous step is immediately filtered, first through a ------ filter and then directly through a Planova 15 N filter. The filters are rinsed with saline to remove all proteins. Filtrate and filter rinse are combined as an intermediate bulk concentrate.

Preparation of bulk finished product; ---------- filtration

Bulk concentrate may optionally be split into two parts before further processing to bulk finished product. The anti-D concentration is adjusted to meet a specification of the 300 µg dosage (1500 IU). Then NaCl is added, if needed, to a calculated minimal final concentration of -----, glycine content is adjusted to ------, Albumin (Human) is added to a final concentration of 10 mg/mL, and WFI is added to reach the final concentration. The pH is adjusted to ---. Bulk finished product is filtered through a ------- membrane filter into a pre-sterilized container.

Filling of the bulk finished product into glass syringes

Sterile-filtered pressurized nitrogen is used to sterile filter the final formulated bulk finished product into a sterilized glass surge vessel. The final formulated bulk finished product solution is aseptically filled into glass syringes by the contract manufacturer, Vetter Pharma-Fertigung GmbH (Ravensburg, Germany). Each syringe is checked for acceptable fill volume and cosmetic and critical damage, and is stored under controlled temperature and security conditions at Vetter.

Finished product specifications

Appearance	IgG	PKA
Total protein	IgA	Pyrogen
Glycine	Monomers + Dimers	General safety
Albumin	Aggregates (polymers)	Sterility
Sodium	Fragments	Anti-D antibody
Chloride	pH	Anti-A isoagglutinins

Aluminum	Osmolality	Anti-B isoagglutinins
Triton X-100	Identity	
TnBP	Anticomplementary activity	

Final labeling and packaging

Syringes are visually inspected after storage, and labeled and blister-packed at Vetter. The lot number and expiry date are printed on the label and the blister foil. The blister package, including a needle, and the package insert are packed into a carton box at Vetter. The lot number and expiry date are printed on the box.

Stability Studies

The stability of two intermediates in the Rhophylac® manufacturing process, i.e., Rhophylac® Bulk Concentrate solution and the Rhophylac® Bulk Final Product, has been studied. The stability study of Rhophylac® Bulk Concentrate was designed to cover the possibility of storage of the intermediate product for -----days prior the final formulation step. This study performed on three lots of Rhophylac® Bulk Concentrate showed that the stability of the intermediate product is not affected by such storage.

The stability study of Rhophylac® Bulk Final Product covers the stability of the bulk finished product solution in transport vessels. The tested temperatures and the time scale represented the worst-case situation of storage and transport of Rhophylac® Final Bulk. The results obtained in this study show that the stability of the final bulk solution is not affected by the transport and storage in stainless steel vessels.

Stability studies of the final product are ongoing. The analytical test procedures applied during stability studies are listed below: (Some parameters are not tested at all intervals)

Appearance	IgA
Anti-D Content	Albumin
Total Protein	TnBP
pH	Triton X-100
Anticomplementary activity	Sodium
Osmolality	Chloride
Glycine	Anti-A isoagglutinins
PKA	Anti-B isoagglutinins
Identity	Density
Residual nitrogen	Sterility
Pyrogen	General safety

The data obtained after --------- of storage at 5 ± 3 °C remain within specifications, and support the stability of the product under recommended storage condition (2 – 8 °C). The date of manufacture is defined as the first sterile filtration of the formulated drug product. Additional lots of Rhophylac® will be put on an updated long-term stability program (----------) to support a dating period of 36 months.

Lot Release

Samples from final product lots have been analyzed by the FDA and found to be satisfactory. The product will be subject to lot-by-lot release.

Establishment Inspection

A pre-approval inspection of ZLB Bioplasma AG final-product production facility in Bern, Switzerland and Vetter Pharma-Fertigung AG in Ravensburg, Germany were conducted. All establishments were found to be in compliance with current good manufacturing practice standards.

Enviromental Assessment

ZLB Bioplasma AG has been granted a categorial exclusion from an Enviromental Assessment under 21 CFR 25.31 (c).

IV. Pharmacology

The mechanism by which Rh_o(D)Immune Globulin suppresses immunization to Rho(D)-positive red blood cells is not completely known. In a clinical study with Rh_o(D)-negative healthy male volunteers, both the IV and IM administration of Rhophylac® 1500 IU (300 μg) at 24 hours after injection of 15 mL of Rh_o(D)-positive red blood cells resulted in an effective clearance of Rh_o(D)-positive red blood cells. While the IV administration of Rhophylac® caused an instant onset of red blood cell disappearance, the onset of elimination of red blood cells following IM administration was delayed, as anti-Rh_o(D) IgG had to be released from the injection site into the bloodstream. 99% of injected red cells were cleared within 12 hours after IV administration. After IM administration, a similar degree of red cell clearance was measured after 144 hours.

Following IV injection in pregnant Rh_o(D)-negative women, peak serum levels ranged from 62 to 84 ng/mL after one day. Following IM injection, peak serum concentrations of anti-Rh_o(D) IgG ranged from 6.9 to 46.1 ng/mL and were achieved between 2 and 7 days. Regardless of the route of administration, anti-D IgG was measurable in all women up to at least 9 weeks following administration of Rhophylac®. The mean elimination half-life was determined to be approximately 17.5 days.

In a clinical study of 14 Rh_o(D)-negative women, a single injection of Rhophylac® 1500 IU (300 μg) was administered either intravenously or intramuscularly at week 28 of gestation and anti-Rh_o(D) IgG serum levels were measured until 11 weeks. Six women received Rhophylac® intravenously and 8 women received Rhophylac® intramuscularly. Following IV injection, the mean systemic clearance was 0.20 ± 0.03 mL/min and half-life was 16 ± 4 days. Following IM injection, peak serum concentrations of anti-Rh_o(D) IgG ranged from 7 to 46 ng/mL and were achieved between 2 and 7 days. The mean clearance was 0.29 ± 0.12 mL/min and half-life was 18 ± 5 days. The absolute bioavailability of IM administration was 69%. Regardless of the route of administration, anti-D IgG titers were measurable in all women up to at least 9 weeks following administration of Rhophylac®.

V. Medical

Clinical Overview

Rhophylac® is a liquid anti-D immune globulin G (IgG) intended for the prevention of Rhesus immunization in Rh_o(D)-negative women both antepartum and postpartum, for prophylaxis following incidents and interventions during pregnancy, and for Rhesus incompatible transfusion of red blood cells. Clinical data presented in this Biologic License Application (BLA) support the administration of 300 µg Rhophylac® either IM or IV at 28 weeks of gestation and within 72 hours of delivery of a Rh_o(D)-positive child.

The primary claims for this application are supported by the clinical results from the pivotal study, ZLB 98_011. Clinical data from this study demonstrate that none of the Rh_o(D)-negative women treated with Rhophylac® who delivered a Rh_o(D)-positive child were immunized to Rh_o(D). Efficacy was seen in women who received 300 µg of Rhophylac® either IM or IV. The clinical results of study ZLB 98_011 are supported by data from the pharmacokinetic study ZLB 98_012 where all Rh_o(D)-negative women treated with Rhophylac® were protected from Rhesus immunization following delivery of a Rh_o(D)-positive infant.

Overall, Rhophylac® was well tolerated. There were no reports of anaphylaxis or serious allergic reactions with either route of administration. The majority of adverse events were symptoms related to the underlying pregnancy. Most serious adverse events were hospitalizations for pregnancy and/or labor-related symptoms; none were considered related to Rhophylac®. There was no evidence that administration of Rhophylac® was associated with transmission of viruses. In addition to these completed studies, ZLB conducted a study in healthy males comparing the ability of Rhophylac® manufactured at the old and new production facilities to remove Rh_o(D)-positive RBCs and also to prevent Rhesus immunization.

In summary, clinical data from ZLB 98_011 demonstrate that treatment with Rhophylac® either IM or IV prevents Rh_o(D) immunization in Rh_o(D)-negative women who deliver a Rh_o(D)-positive child.

Pharmacology

Pharmacokinetic data for 300 µg Rhophylac® administered IV or IM in pregnant women were generated in Study ZLB 98_012. The aim of the study was to obtain evaluable pharmacokinetic data after IM and IV administration of 300 µg of Rhophylac® from at least 6 pregnant RhD-negative women for each route of administration. Fifteen patients were enrolled; 7 patients received 300 µg Rhophylac® IV and 8 received Rhophylac® IM.

The following conclusions can be drawn from the pharmacokinetic analyses of Rhophylac® administered IV or IM to pregnant RhD-negative women in study ZLB 98_012.

- IV administration of Rhophylac® provides less variable serum concentrations of anti-D IgG than IM administration. The inter-subject variability seen with IM administration reflects individual differences in uptake of antibody from muscular deposits.

- Following IM administration of Rhophylac®, peak serum concentrations of anti-D IgG were achieved between 2 and 7 days. Body weight appears to have an effect on uptake of anti-D IgG when administered IM.

- Regardless of the route of administration, quantifiable anti-D IgG serum concentrations were observed in all patients up to at least 9 weeks following administration of Rhophylac®.

- Mean serum anti-D IgG concentrations differed significantly up to 7 days following IV and IM administration of 300 µg Rhophylac®. However, after 2 to 3 weeks following either IV or IM administration of Rhophylac® there was no significant difference in the mean serum levels.

- The terminal elimination half-lives were almost identical for both IV and IM administration of Rhophylac®.

- The bioavailability of the IM administration was determined to be 68.7%. When patients whose weight exceeded 80 kg were excluded from the calculation, the bioavailability increased to 79.0%.

Efficacy

The efficacy of 300 µg Rhophylac® to prevent Rhesus immunization has been demonstrated in 2 clinical studies, ZLB 98_012 and ZLB 98_011. The following conclusions can be made from these two studies:

- Results from these two studies demonstrate that administration of 300 µg Rhophylac® IV or IM at week 28 gestation and within 72 hours postpartum prevents immunization to Rh_o(D).

- In the pharmacokinetic study, ZLB 98_012, none of the patients who received 300 µg Rhophylac® either IV or IM at week 28 gestation and within 72 hours postpartum became immunized to Rh_o(D) antigen.

- In the pivotal study, ZLB 98_011, in the Rh_o(D)-negative women who delivered a Rh_o(D)-positive infant, none of the women had detectible anti-D IgG at their follow-up visit.

- There was no difference in the efficacy outcome measures between the IV and IM route of administration or between the two lots of Rhophylac® studied.

Safety

In the 3 clinical studies, 592 women received at least one dose of Rhophylac®. Review of the safety events for all three studies demonstrate that administration of Rhophylac®, either by the IV or IM route, is well tolerated.

- The majority of adverse events reported in the three studies resulted from pregnancy or labor.

- Adverse events considered related to Rhophylac® are those known to occur with administration of anti-D, e.g., pain at injection site, itching, headache, etc. These adverse events were considered to be of mild or moderate severity.

- There were no reports of anaphylaxis or serious allergic reactions due to Rhophylac®.

- All serious adverse events reported for either mothers, fetuses, or newborns were considered by the investigator unrelated to study drug. The majority was associated with pregnancy or labor.

- The occurrence of adverse events was similar between the two routes of administration of 300 µg Rhophylac®. In study ZLB 98_011, the two lots of Rhophylac® had a similar safety profile.

- There was no evidence of viral transmission by Rhophylac® of HAV, HBV, HCV, CMV, HIV-1/2, or parvovirus B19. The frequency of seroconversion to CMV in study ZLB 98_011 was consistent with the expected rate of seroconversion for the study population.

Conclusions

Rhophylac® is an anti-D immune globulin product that contains 300 µg of anti-D IgG. Anti-D IgG has been available for the prevention of $Rh_o(D)$ immunization and treatment after incompatible infusions for more than 30 years. The efficacy of anti-D immune globulin products has been well-established. Therefore, a clinical development program evaluating safety and efficacy of Rhophylac® only in the population for whom treatment is the primary indication, i.e. routine prophylaxis in $Rh_o(D)$-negative pregnant women, was considered adequate to allow extrapolation of effect to the other smaller patient populations for whom treatment with anti-D IgG would be indicated. In addition, the pharmacokinetics of Rhophylac® after IV and IM injection was studied in the target population. For complications of pregnancies (e.g., interventions or incidents during pregnancy), no clinical data are presented from clinical studies. To determine the anti-D IgG doses needed for women with excessive feto-maternal hemorrage, the number of Rho(D)-positive fetal red blood cells should be determined by the Kleihauer-Betke test or another suitable test. The final dose is then calculated based on the finding that 20 µg of anti-D IgG neutralize 1 mL of Rho(D)-positive red blood cells.

Rhophylac® pharmacodynamic activity was investigated in a study (ZLB 621) with healthy $Rh_o(D)$-negative male volunteers who were challenged with $Rh_o(D)$-positive RBCs. Although this study is not included in the BLA as it was performed with the 200 µg dose of Rhophylac® and a challenge of only 5 mL of $Rh_o(D)$-positive RBCs, this study demonstrated that Rhophylac® rapidly eliminated $Rh_o(D)$-positive RBC in $Rh_o(D)$-negative subjects and prevents their $Rh_o(D)$-immunization.

For the postpartum prevention of $Rh_o(D)$ immunization, a clinical study with the 200 µg dosage form of Rhophylac® (ZLB 622) was performed. The efficacy results from this study suggest that

none of the 139 eligible women developed antibodies against the Rh_o(D)-antigen. This study is regarded to be supportive and the study report is included in the BLA.

The pivotal study ZLB 98_011 and the pharmacokinetic study ZLB 98_012 were performed with the 300 µg dose of Rhophylac® and addressed the ante- and post-partum prophylactic treatment. The studies showed that Rhophylac® was effective in preventing Rh_o(D) immunization, as none of the total of 256 efficacy-evaluable women (248 from the pivotal study ZLB 98_011 and 8 women from study ZLB 98_012) became Rh_o(D) immunized, as assessed by the absence of anti-D antibodies at 6 to 11.5 months postpartum. In addition, study ZLB 98_011 demonstrated that both lots of Rhophylac® evaluated were equally efficacious, safe, and well-tolerated when given IV or IM. The pharmacokinetic study showed that both routes of administration resulted in comparable anti-D IgG serum levels after 2 to 3 weeks following administration, until term.

Due to the manufacturing procedure, Rhophylac® is expected to be a safe formulation in terms of tolerability and viral safety. The safety and tolerability of Rhophylac® were confirmed in both the *in vitro* and clinical studies. Rhophylac® was well tolerated in clinical studies when administered IV or IM, and the tolerability of Rhophylac® has been well documented since its market introductions in both Switzerland and Germany. With more than 100,000 units of Rhophylac® sold, only four spontaneous reports of probably- or possibly- related adverse events were reported to ZLB`s pharmacovigilance unit. The adverse events consisted of rash, pruritus, tachycardia, chills, rigors, fever, nausea, fatigue, and headache.

Allergic reactions are generally rare for anti-D immune globulins. In patients with known hypersensitivity to homologous immune globulins or known hypersensitivity to any of the excipients, Rhophylac® is contraindicated. Although Rhophylac® had been shown to have a high purity, the presence of trace amounts of IgA cannot be excluded. Rhophylac® is contraindicated in patients with IgA deficiency. The physician must weigh the benefit of treatment with Rhophylac® against the potential risks of hypersensitivity reactions.

VI. Labeling

The labeling of the product is adequate; the product pharmacology, recommended uses, dosing and administration procedures, and possible adverse reactions are sufficiently described.

LICENSING REVIEW COMMITTEE

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