INFORMATION FOR PATIENTS:

What does this package leaflet enclose?
This leaflet gives you the details of the medicine that will be given to you. The details will be regarding the contents of the medicine, how to use it, and what side affects you should be careful about.

What is Anti D?
Recombinant Anti Rho-D Immunoglobulin contains– Anti Rho-D Immunoglobulin as active ingredient.

Which case this medicine should be used?
Recombinant Anti Rho-D Immunoglobulin is indicated to prevent Rho-D negative women from forming antibodies to fetal rhesus positive red blood cells that may pass into the maternal blood during childbirth, abortion or certain other sensitizing events.

Which information you must know before taking Recombinant Anti Rho-D Immunoglobulin?
You should not take Recombinant Anti Rho-D Immunoglobulin if any of the following apply to you.
! History of allergic symptoms or hypersensitivity to human immunoglobulin.

Care should be taken:
Recombinant Anti Rho-D Immunoglobulin if used use after delivery, should be given intramuscularly only in the mother. Recombinant Anti Rho-D Immunoglobulin should not be given to the newborn.
The mother should be observed for at least 20 minutes after administration.
Children: This medicine in not for children.
With other medicinal products/ food or beverages:
Recombinant Anti Rho-D Immunoglobulin has not been studied for interactions with other medicines. It is given in hospital after your delivery. No food interactions have been known. Tell your doctor if you are taking any other medications.
Pregnancy and Lactation
Recombinant Anti Rho-D Immunoglobulin does not harm the fetus or affect future pregnancies or the reproduction capacity of the maternal recipient. No studies have been done during lactation.
Sports or Effects on ability to drive and use machine
The effect on sports or ability to drive is not known.
The effects of excipients are not known. But they may cause allergic reactions in certain individuals. If any unusual signs or symptoms occur, then immediately inform your doctor.

How to take Recombinant Anti Rho-D Immunoglobulin? Instruction for good use:
Recombinant Anti Rho-D Immunoglobulin should always be given to mothers with blood group Rh negative means who do not have Rh antibodies, in their blood and who have just delivered infants with blood group Rh positive means who have Rh antibodies.
You will receive the medicine if you are Rh negative blood group and pregnant to protect you from sensitization to Rh antibodies.
Recombinant Anti Rho-D Immunoglobulin should not be given to the infant and to Rho-D positive individuals.
If you have taken more Recombinant Anti Rho-D Immunoglobulin
Recombinant Anti Rho-D Immunoglobulin as it is given by your doctor hence very rare chance of getting more drug. There is no report of overdose received by the marketing company.
If you forget taking Recombinant Anti Rho-D Immunoglobulin.
Recombinant Anti Rho-D Immunoglobulin should be given within 72 hours of delivery. It is given by your doctor during the pregnancy or after delivery. The effectiveness of dose after 3 days of delivery is not known.
If you stop taking Recombinant Anti Rho-D Immunoglobulin.
Recombinant Anti Rho-D Immunoglobulin is given only once as soon as possible after the delivery or during the pregnancy based on physician decision.

What are the possible side effects?
There are no known side effects. However local pain, fever, flushing, headache and chills may occur on administration.
Side effects of excipients are not known. They may cause allergic reactions depending on individual. If any unusual signs or symptoms occur, then immediately inform your doctor.

How to store Recombinant Anti Rho-D Immunoglobulin?
Recombinant Anti Rho-D Immunoglobulin should be stored under refrigeration at 2°C to 8°C and should not be freeze. Keep out of sight of children.
Do not use after the time limitation indicated on the package box. The expiry date refers to the last day of the indicated month.
Shelf life of the Recombinant Anti Rho-D Immunoglobulin is 24 months.
Medicinal product after opening should be used immediately and unused liquid should be discarded.
If the package is damaged or seal opened, then do not use the medication. The medicine should be discarded by your doctor as per hospital or clinic procedure. It should not be thrown in sewage or domestic dirt.

For Patient Counseling Information (or Patient Information) Refer Full Prescribing information.

To report Suspected Adverse Reactions, contact Bharat Serums and Vaccines at pv@bharatserums.com or visit the website www.bharatserums.com/adverse.html

BSV

IN90417D0PFS

For the use only of a Registered Medical Practitioner or a Hospital or a Laboratory.

RECOMBINANT ANTI RHO-D IMMUNOGLOBULIN INJECTION 300 MCG

अँटीडी AntiD® 300 mcg / 1mL

Vial or Pre-filled syringe (PFS)
(Liquid Injection)
For Intramuscular Injection only

QUALITATIVE AND QUANTITATIVE COMPOSITION:
Each vial / Pre-filled syringe contains:
Recombinant Anti Rho-D Immunoglobulin 300 mcg / ml.
Excipients:
Glycine I.P. 30 mg, Sodium Chloride I.P. 5.84 mg, Water for Injection I.P. q.s. to 1.0 ml.
The Anti Rho-D immunoglobulin content is expressed as mcg per dose. It can also be expressed as International Units (IU) per dose. The conversion factor is 1 mcg = 5 IU.

PHARMACEUTICAL FORM:
Recombinant Anti Rho-D immunoglobulin preparation is a clear, colorless, and sterile solution.

DESCRIPTION:
Recombinant Anti Rho-D Immunoglobulin is a clear, sterile solution containing recombinant antibodies reactive to Rh D positive red cells. Recombinant Anti Rho-D Immunoglobulin is produced by recombinant technology using genetically engineered Chinese Hamster Ovary (CHO) cells; purified using protein affinity chromatography and used in preventing Rh immunization. Recombinant Anti Rho-D Immunoglobulin preparation contains IgG anti-D (anti-Rh) for use in preventing Rh immunization. These are antibodies that bind and cause destruction of foetal Rh D positive red blood cells that have passed from the foetal circulation to the maternal circulation. Therefore, in a Rh-negative mother it can prevent sensitization of the maternal immune system to Rh D antigens, which can cause rhesus disease in the current or in subsequent pregnancies.

PHARMACOLOGICAL PROPERTIES:
Description & Pharmacotherapeutic group.
ATC code: J06BB01 anti-D (rh) immunoglobulin.

Mechanism of Action:
Recombinant Anti Rho-D Immunoglobulin is protein with a molecular weight of 150 kD and is stabilized with excipients to ensure the stability till the end of shelf life of 24 months from the date of manufacturing.
Recombinant Anti Rho-D Immunoglobulin act by suppressing the immune response of Rh-negative individual to Rh positive red blood cells and hence prevents alloimmunization. Passive administration of r – anti D causes rapid non - inflammatory clearance of passive anti D coated red blood cells, which stops the inflammatory destruction of fetal red blood cells, evoking a natural immune response. Additionally, suppression of the immune response lead to the down regulation of maternal immature dendritic cells or anti D specific B cells before the anti D response develops.

Pharmacodynamic properties:
Recombinant Anti Rho-D Immunoglobulin coated red cells are rapidly cleared from the maternal blood. Recombinant Anti Rho-D Immunoglobulin is known to mediate Antibody- Dependent Cell Mediated Cytotoxicity (ADCC). Mononuclear phagocytic system is also thought to be responsible for clearance of anti-D-sensitized erythrocytes. There is more evidence building up in recent years that ADCC may not be the primary mode of red cell clearance in vivo. Antibody mediated B-cell inhibition is emerging as the possible mechanism for red cell clearance.
Inhibition of B cells by crosslinking heterologous receptors (co-inhibition):
! FcγRIIb inhibitory activity requires bridging to specific co-targets.
! Inhibition many activate pathways in both healthy and diseased B cells.
! Could result in potent suppression of B-cell responses without destroying B cells.

Pharmacokinetic properties:
The PK parameters of Recombinant Anti Rho-D Immunoglobulin are expected to be like a biologically similar preparation of monoclonal anti-D:
Pharmacokinetic parameters of monoclonal anti-D are as follows: Median T_{max} (h) - 168, Mean C_{max} (ng/mL) 42.83, Mean AUC0→t (ng.h/mL) 30241.71, AUC0→∞ (ng.h/mL)

Preclinical Safety Data:
Toxicity studies were done on animals – rats, mice, rabbits, and dogs. Single dose toxicity, acute toxicity and repeat dose toxicity studies have been performed. All safety and toxicity studies show no adverse effect in animals.

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Toxicity:
Acute toxicity studies of r – anti D were conducted on Swiss Albino mice using single dose of 2400 mcg/kg body weight, administered either intramuscularly or subcutaneously. Similar studies were performed using Wistar rats. These rodents were observed for clinical signs of toxicity, body weight and mortality, for a period of 14 days. Treated rodents did not reveal treatment attributed behavior alterations, clinical signs, gross pathological abnormalities, preterminal deaths and adverse effects on body weight gain. In conclusion, r – anti D is safe substance for given dose level of 2400 mcg/kg body weight in treated rodents when administered intramuscularly or subcutaneously.

Repeat dose toxicity study was performed in Wistar rats at selected doses of 15, 50, and 150 mcg/kg administered intramuscularly over a period of 14 days. Repeat dose administration did not show any clinical signs and mortality in any of the treated animals. The body weight gain, hematological parameters and clinical biochemistry parameters in all the treatment groups were comparable with control group animals. Gross pathology and histopathology did not reveal any significant changes related to treatment at 150 mcg/kg body weight/day when compared with control group animals. It was concluded, No Observed Adverse Effect Level (NOAEL) for Recombinant Anti Rho-D Immunoglobulin is 150 mcg/kg body weight in rats.

Similar results were observed in repeat dose toxicity study conducted on New Zealand White Rabbits at a dose of 15, 50, 150 mcg/kg administered intramuscularly over a period of 14 days.

Repeated dose toxicity study on Beagle Dogs at a dose of 1500 and 2000 mcg/dog/day for 14 consecutive days had no effect on general health of the animal. There were no toxicity signs, changes in body weight, feed consumption, haematology and clinical chemistry parameters. It was concluded that No Observed Adverse Effect Level (NOAEL) for Recombinant Anti Rho-D Immunoglobulin is 2000 mcg/dog/day.

The allergenicity study in Guinea pigs to estimate sensitizing potential of r-anti D was conducted. There was no skin reaction observed at topical challenge exposure site. The reaction score found was 0 - 8 % i.e. grading-1, hence r-anti D Immunoglobulin was classified as a weak sensitizer.

Carcinogenicity and genotoxicity
IgG is a normal constituent in human plasma and has not been reported to be associated with any embryo-foetal toxicity or oncogenic/ carcinogenic potential. No study was done for evaluating carcinogenicity or genotoxicity.

CLINICAL PARTICULARS:
Therapeutic indications (Approved)
Recombinant Anti Rho-D Immunoglobulin is indicated to prevent Rh negative women from forming antibodies to foetal rhesus positive red blood cells, that may pass into the maternal blood during child birth, abortion or certain other sensitizing events.

Posology and method of administration:
- Recombinant Anti Rho-D Immunoglobulin should always be given to rhesus negative mothers with no anti-D antibodies in their serum and who have just delivered rhesus positive infants. A dose of 300 mcg should be given intramuscularly as soon as possible within 72 hours after delivery.
- It is recommended that in cases of abortion or termination of pregnancy, the Rh-negative women should be given 150 mcg of Recombinant Anti Rho-D Immunoglobulin within 72 hours, if the pregnancy is of 12 weeks duration or less. In cases of miscarriage in an advanced stage of pregnancy, 300 mcg should be administered within 72 hours.
- Other sensitizing events during pregnancy in Rh negative women at a risk of transplacental haemorrhage and not known to have been sensitized should begiven 150 mcg or 300 mcg of Recombinant Anti Rho-D Immunoglobulin.

Method of administration:
- Route of administration - Intramuscular administration.

The administration of Recombinant Anti Rho-D Immunoglobulin should be performed under the supervision of a physician.

Contraindications:
Recombinant Anti Rho-D Immunoglobulin is contraindicated in:
- Pregnant woman with positive ICT (Indirect Coombs' test)
- Pregnant woman is Rh–D positive
- Should not be given to an infant.

Drug to Drug interactions:
No drug-to-drug interactions studies were conducted with Recombinant Anti Rho-D Immunoglobulin.

Special warnings and precautions for use:
- Recombinant Anti Rho-D Immunoglobulin is for intramuscular use only, do not inject intravenously.
- The product is intended for maternal administration.
- Do not inject the new-born infant.
- Administer with caution to patients who have had prior severe systemic allergic reactions to human immunoglobulin.

Specific Population Use:
Pregnancy and Lactation:
Recombinant Anti Rho-D Immunoglobulin does not harm the fetus or affect future pregnancies or the reproduction capacity of the maternal recipient. This medicinal product is intended for use in other sensitizing events during pregnancy. No studies have been done during lactation.

Effects on ability to drive and use machine:
No data available.

Geriatric use:
It is not indicated in Geriatric use.

Renal & Hepatic impairment:
No study done on renal and hepatic impairment condition.

Undesirable effects/ Adverse Reactions (Common, Uncommon, Rare):
- Injection site reactions include swelling, induration, redness and mild pain or warmth.
- Fever, flushing, headache, and chills may rarely occur.
- Adverse events noted in the clinical study were pyrexia, abdominal pain, pruritus, hypertension, hypotension, abnormal White Blood Cell counts.
- Clinical experience adverse events seen during Phase III clinical study

In Anti D phase 3 study following adverse events were observed:

Adverse reaction System Organ Class Preferred Term	Recombinant Anti Rho-D Immunoglobulin (n= 144)	Rhogam (n=71)
Any	4	4
General disorders and administration site conditions Pyrexia		
Gastrointestinal disorders, Abdominal pain	2	0
Skin and subcutaneous tissue disorders Pruritus	0	1
Vascular disorders, Hypertension	0	1
Hypotension	0	2
Investigations White blood cell counts abnormal	1	0

Post marketing experience adverse events:
No data available of post-marketing experience.

Overdose:
Overdosage can lead to any adverse events as listed above. No antidote for this drug. The stoppage of drug administration shall ameliorate the symptoms gradually.

CLINICAL STUDIES:
A prospective, randomized clinical trial to confirm safety and efficacy of recombinant anti-D immunoglobulin in prevention of isoimmunization in comparison with polyclonal anti-D immunoglobulin r-anti D was conducted in total of 215 subjects; 144 subjects were randomized to receive the recombinant anti D (Test group) and 71 subjects were randomized to receive polyclonal anti D (RhogamR) (Reference group).

Each eligible subject received a single intramuscular injection either the Test or Reference anti-D IgG within 72 hours of delivery. Insignificant p value for Indirect Coomb's Test (ICT) for Day 90 (p=0.30) and Day 180 (p=0.49) was observed between Test and Reference in prevention of Rh iso-immunization in Rh (D) negative pregnant women delivering Rh (D) positive infant. Four subjects from each group experienced 1 adverse event. All the adverse events were mild in severity. No subject receiving Test developed antibodies to r-anti D post administration of drug. This study observed equal efficacy between Test and Reference as sensitization (as evaluated by positive ICT at Day 90 or 180) was not noted in any subject in both the groups. The safety profile was same in both groups with mild severity.

PHARMACEUTICAL PARTICULARS:
- ***Shelf life*** - 24 months from date of manufacturing.
- ***Special precautions for Storage, Handling & Disposal*** - Store at 2°C to 8°C. Do not freeze.
- ***Nature and contents of container*** - A glass vial or PFS containing clear, colourless and sterile liquid having Recombinant Anti Rho-D Immunoglobulin activity of 300 mcg.

MARKETED BY:
Bharat Serums and Vaccines Limited
17th Floor, Hoechst House, Nariman Point, Mumbai – 400 021, India.

MANUFACTURED BY:
Bharat Serums and Vaccines Limited
Plot No. K-27, Anand Nagar, Jambivili Village, Additional MIDC, Ambernath (East) - 421501, Tal: Ambernath City, Dist.: Thane-Zone6, Maharashtra, India

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