For the use only of a Registered Medical Practitioner or a Hospital or a Laboratory only.
℞ *READ PACKAGE INSERT CAREFULLY BEFORE USE PRESCRIBING INFORMATION*

TRINBELIMAB INJECTION 150 MCG / 300 MCG

AntiD®

Vial / PFS
(Liquid Injection)
For Intramuscular Injection only

For sale in India only

Trinbelimab is the WHO INN name of "Recombinant Anti Rho-D Immunoglobulin"

1. Generic Name:
Trinbelimab Injection.

2. Qualitative and Quantitative Composition:
Each Vial / PFS contains:
Trinbelimab (Purified Liquid Bulk) 150 mcg/ml and 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.
Trinbelimab Injection 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.

3. Dosage form and strength:
Dosage form: Liquid Injection, clear, non-pyrogenic, colorless and sterile solution.
Strength: 150 mcg/ml and 300 mcg/ml.

4. Clinical particulars:
4.1. Therapeutic Indication:
Trinbelimab Injection 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 pregnancy, childbirth, abortion or certain other sensitizing events.

4.2. Posology and method of administration:
Dosage and Administration:

Indication	Dose	Notes
Pregnancy and other obstetrical conditions		
Postpartum (if the newborn is Rh-positive) Administer within 72 hours of delivery. Antepartum: - Prophylaxis at 26 to 28 weeks gestation if ICT result is negative. Administer within 72 hours of suspected or proven exposure to Rh-positive red blood cells resulting from: - Amniocentesis, chorionic villus sampling (CVS) and percutaneous umbilical blood sampling (PUBS). - Abdominal trauma or obstetrical manipulation. - Ectopic pregnancy. - Threatened pregnancy loss after 12 weeks gestation with continuation of pregnancy - Pregnancy termination (spontaneous or induced) beyond 12 weeks gestation.	Trinbelimab Injection 300 mcg / 1500 IU	Additional doses of Trinbelimab are indicated when the patient has been exposed to > 15 mL of Rh-positive red blood cells. This may be determined by use of qualitative or quantitative tests for fetal-maternal hemorrhage. If antepartum prophylaxis is indicated, it is essential that the mother receive a postpartum dose if the infant is Rh-positive. If Trinbelimab is administered early in pregnancy (before 26 to 28 weeks), there is an obligation to maintain a level of passively acquired anti-D by administration of Trinbelimab at 12-week intervals.
Actual or threatened termination of pregnancy (spontaneous or induced) up to and including 12 weeks gestation.	Trinbelimab Injection 150 mcg / 750 IU	Trinbelimab to be administered within 72 hours of exposure.

Method of Administration:
- Route of administration - Intramuscular administration in the deltoid.

The administration of Trinbelimab Injection should be performed under the supervision of a physician.

4.3. Contraindications:
Trinbelimab Injection is contraindicated in:
- Pregnant woman with positive ICT. (Indirect Coombs' test)
- Pregnant woman is Rh-D positive.
- Should not be given to an infant.

4.4. Special warnings and precautions for use:
- Trinbelimab Injection 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.

4.5. Drug interactions:
No drug-to-drug interactions studies were conducted with Trinbelimab Injection.

4.6. Use in special populations:
Pregnancy and Lactation:
Trinbelimab Injection 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.

Geriatric Use:
It is not Indicated in Geriatric use.

Renal and Hepatic Impairment:
No study done on renal and hepatic Impairment Condition

4.7. Effects on ability to drive and use machines:
No Data available.

4.8. 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 Trinbelimab Injection phase 3 study following adverse events were observed:**

Adverse reaction System Organ Class Preferred Term	**Trinbelimab (n=144)**	**Rhogam (n=71)**
Any.	4	4
General disorders and administration site conditions Pyrexia.	1	0
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

- **In Trinbelimab Injection Phase IV study following adverse events were observed:**

	AntiD® [Trinbelimab] 150 mcg (N = 71)	AntiD® [Trinbelimab] 300 mcg (N = 229)	Overall (N = 300)
System Organ Class Preferred Term	**Number of Events**	**Number of Events**	**Number of Events**
Number of Subjects with at least one TEAE	5	29	34
Blood and Lymphatic System Disorders	0	2	2
Anaemia	0	1	1
Leukocytosis	0	1	1
Cardiac disorders	0	1	1
Tachycardia	0	1	1
Gastrointestinal Disorders	0	4	4
Abdominal Pain	0	1	1
Gastritis	0	2	2
Vomiting	0	1	1
General Disorders and Administration Site Conditions	3	11	14
Injection Site Erythema	2	4	6
Injection Site Pain	1	2	3
Injection Site Swelling	0	1	1
Pyrexia	0	4	4
Infections and Infestations	0	1	1
Bacterial Infection	0	1	1
Investigations	0	1	1
White Blood Cell Count Increased	0	1	1
Musculoskeletal and Connective Tissue Disorders	1	2	3
Back Pain	1	1	2
Flank Pain	0	1	1
Nervous System Disorders	0	2	2
Headache	0	2	2
Pregnancy, Puerperium and Perinatal Conditions	0	1	1
Pre-Eclampsia	0	1	1
Renal and Urinary Disorders	0	1	1
Dysuria	0	1	1
Reproductive System and Breast Disorders	1	2	3
Nipple Disorder	0	2	2
Vaginal Discharge	1	0	1
Skin and Subcutaneous Tissue Disorders	0	1	1
Hyperhidrosis	0	1	1

4.9. 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.

5. Pharmacological properties:
Description & Pharmacotherapeutic group.
ATC code: J06BB01 Anti-D (Rh) immunoglobulin

5.1. Mechanism of Action:
Trinbelimab Injection 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.

Trinbelimab Injection act by suppressing the immune response of Rh-negative individual to Rh positive red blood cells and hence prevents alloimmunization. Passive administration of Trinbelimab 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 leads to the down regulation of maternal immature dendritic cells or Anti-D specific B cells before the Anti-D response develops.

5.2. Pharmacodynamic properties:
Trinbelimab Injection coated red cells are rapidly cleared from the maternal blood.
Trinbelimab Injection 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.

5.3. Pharmacokinetic properties:
The PK parameters of Trinbelimab Injection 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 AUC_{0-t} (ng.h/mL) 30241.71, $AUC_{0-\infty}$ (ng.h/mL) 35770, λ (1/h) 0.001, t½ (h) 599 (~25 days), V (L) 7.3.

5.4. Clinical Studies:
AntiD® Phase III study:
A prospective, randomized clinical trial to confirm safety and efficacy of Trinbelimab Injection in prevention of isoimmunization in comparison with polyclonal Anti-D immunoglobulin was conducted in total of 215 subjects; 144 subjects were randomized to receive the Trinbelimab Injection (Test group) and 71 subjects were randomized to receive polyclonal Anti-D (Rhogam) (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 isoimmunization in Rho-D negative pregnant women delivering Rho-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.

AntiD® Phase IV study:
A prospective, multi-centre, phase IV study for post-marketing safety evaluation of Anti-D® in the prevention of maternal Rh-isoimmunization during childbirth, abortion, or certain other sensitizing events was conducted in 300 Rh negative female subjects.
Each of 300 eligible subjects received a single intramuscular injection of Anti-D® either 300 mcg [229 subjects] or 150 mcg [71 subjects] within 72 hours of the sensitizing event. The safety results showed, no death or Serious Adverse Event during the study. About 34 of 54 adverse events (AE) reported were Treatment Emergent Adverse Events (TEAE) from 30 subjects. Of these, 25 subjects and 5 subjects were administered with 300 mcg and 150 mcg of Anti-D® respectively. None of the subjects were discontinued from the study due to any AE's. All the reported AEs were mild in severity except two which were of moderate in severity and completely recovered/resolved. Most of the AEs were unrelated to the study drug. Anti-D® [Trinbelimab] exhibited a favorable safety profile, and no new or unexpected safety signals were identified in the study. Based on the assessment of the adverse events, vital signs, physical examination, and laboratory parameters, Anti-D® [Trinbelimab] administered at a dose of either 300 mcg or 150 mcg did not raise any new or significant safety concerns.

Real-world, observational study in Rh negative pregnant women (RhYTHM study):
The RhYTHM study, examines the real-world scenario of Rh sensitization and immunoprophylaxis utilization among Rh-negative pregnant women in India. The 2nd Interim analysis included 3,745 participants across different regions of India.
Key finding:
- A significant proportion of the participants did not receive appropriate Anti-D prophylaxis.
- The sensitization rate in the study was higher than the global average.
- During previous pregnancies, only 29.5% of eligible participants received Anti-D administration after abortion.
- In current pregnancies, there was an increase in the utilization of antenatal Anti-D prophylaxis compared to past pregnancies.

Safety information on Anti-D in antenatal period:
- Safety in Pregnant Women: The RhYTHM study assessed the safety of Anti-D in 1,513 Rh-negative pregnant women, comparing those who received antenatal Anti-D with those who did not. The study found no significant differences in adverse events between the two groups, suggesting an acceptable safety profile. There were 25 adverse events reported from 3745 participants in the study, but they were deemed similar between the groups receiving and not receiving antenatal Anti-D.

Safety in Neonates:
The study also evaluated the safety of Anti-D in 1,163 neonates born to Rh-negative mothers. The analysis compared the rate of complications in neonates born to mothers who received routine antenatal Anti-D (Group 1, n=268) versus those who did not (Group 2, n=895). The study found a similar rate of complications (approximately 3%) in both groups, indicating an acceptable safety profile for the neonates. The investigators, upon review, concluded that the complications were unrelated to Anti-D administration, attributing them to factors like pre-existing maternal conditions, timing of the injection, and the nature of the complications themselves.

6. Nonclinical properties:
6.1. Animal Toxicology or Pharmacology:
Preclinical Safety Data:
Toxicity studies were performed 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.

Toxicity:
Acute toxicity studies of Trinbelimab Injection 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 behaviour alterations, clinical signs, gross pathological abnormalities, preterminal deaths and adverse effects on body weight gain. In conclusion, Trinbelimab Injection 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 Trinbelimab Injection 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 Trinbelimab Injection is 2000 mcg/dog/day.

The allergenicity study in Guinea pigs to estimate sensitizing potential of Trinbelimab Injection 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 Trinbelimab Injection 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

7. Description:
Trinbelimab Injection is a clear, non-pyrogenic, colorless, sterile solution containing recombinant antibody reactive to Rho-D positive red blood cells (RBCs). Trinbelimab Injection is produced by recombinant DNA technology using genetically engineered Chinese Hamster Ovary (CHO) cells and purified using purification unit operations including chromatography. The purified preparation of Trinbelimab Injection containing IgG Anti-D (Anti-Rh) is used in preventing Rh immunization. The antibody binds and cause destruction of foetal Rho-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 Rho-D antigens, which can cause rhesus disease in the current or in subsequent pregnancies.

8. Pharmaceutical particulars:
8.1. Incompatibilities:
Not Available.

8.2. Shelf-life:
24 months from date of manufacturing.

8.3. Packaging information:
Each PFS pack contains:
Sterile, non-pyrogenic USP Type-I glass prefilled syringe with safety guard & lock-clip, having clear, colorless, solution of Trinbelimab Injection150 mcg/ml or 300 mcg/ml in a plastic tray. The plastic tray containing PFS is placed inside a carton.

Each Vial pack contains:
Sterile, non-pyrogenic USP Type-I glass vial having clear, colorless, solution of Trinbelimab Injection150 mcg/ml or 300 mcg/ml. One blister contains one labeled vial. One Carton contains one unit pack.

8.4. Storage and handing instructions:
Store at 2°C to 8°C. Do not freeze.

Instruction for Handling of PFS with Safety guard & Lock-Clip:
1. Hold the syringe upright by one hand and remove needle cap using other hand.
2. The Syringe is now ready for administration.
3. Note: - Hold the syringe by placing fingers in contact with syringe barrel through windows in safety shield while administration (Fig.1)

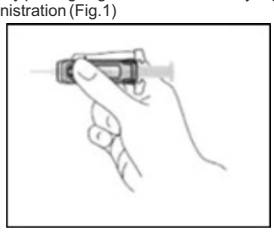

Fig.1

4. After injection, pull out the Lock- clip and slide safety guard over needle.
5. An audible "click" sound indicates proper activation (Fig 2).

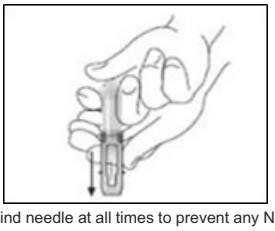

Fig.2

6. Note: - Keep hands behind needle at all times to prevent any Needle stick injury during & after administering injection.

9. Patient Counselling Information:

9.1. What is Anti-D?

Trinbelimab Injection is a clear, non-pyrogenic, colorless, sterile solution containing recombinant antibody reactive to Rho-D positive red blood cells (RBCs).

9.2. Which case this medicine should be used?

Trinbelimab Injection 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.

9.3. Which information you must know before taking Trinbelimab Injection?

You should not take Trinbelimab Injection if any of the following apply to you

- History of allergic symptoms or hypersensitivity to human immunoglobulin.

9.4. Care should be taken:

Trinbelimab Injection if used use after delivery, should be given intramuscularly only in the mother. Trinbelimab Injection 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:

Trinbelimab Injection has not been studied for interactions with other medicines. It is given in hospital after delivery. No food interactions have been known.
Doctors should be informed if patient is taking any other medications.

Pregnancy and Lactation:

Trinbelimab Injection does not harm the fetus or affect future pregnancies or the reproduction capacity of the maternal recipient. No studies were carried out on lactating mothers.

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.

9.5. How to take Trinbelimab Injection? Instruction for good use:

Trinbelimab Injection 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.
Trinbelimab Injection should not be given to the infant and to Rho-D positive individuals.

If you forget taking Trinbelimab Injection.

Trinbelimab Injection should be given within 72 hours of delivery. It is given by your doctor by injecting the medication into muscles during the pregnancy or after delivery. The effectiveness of dose after 3 days of delivery is not known. Trinbelimab Injection is given only once as soon as possible after the delivery or during the pregnancy based on physician decision.

9.6. Warnings and precautions:

- Trinbelimab Injection 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.

9.7. 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.

9.8. Reporting of side effects:
You can report any suspected adverse reactions associated with the use of health products to your doctor and to Bharat Serums and Vaccines Ltd. at mail to: pv@bsvgroup.com or visit the website https://www.bsvgroup.com/adverse/

9.9. How are you given Trinbelimab Injection?
Route of administration - Intramuscular administration.
The administration of Trinbelimab Injection should be performed under the supervision of a physician.

9.10. If you are given more Trinbelimab Injection than you should have been given?
Trinbelimab Injection as it is given by your doctor hence very rare chance of getting more drug. There is no report of overdose received till now.

9.11. How to store?
Trinbelimab Injection should be stored under refrigeration at 2°C to 8°C and should not be freeze. Keep out of reach 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 Trinbelimab Injection 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.

9.12. What Trinbelimab Injection looks like and contents of the pack:
- **Each PFS pack contains:**

Sterile, non-pyrogenic USP Type-I glass prefilled syringe with safety guard & lock-clip, having clear, colorless, solution of Trinbelimab Injection 150 mcg/ml or 300 mcg/ml in a plastic tray. The plastic tray, containing PFS is placed inside a carton.

- **Each Vial pack contains:**

Sterile, non-pyrogenic USP Type-I glass vial having clear, colorless, solution of Trinbelimab Injection 150 mcg/ml or 300 mcg/ml. One blister contains one labeled vial. One Carton contains one unit pack.

- **Active ingredient:** Trinbelimab (Purified liquid bulk) 150mcg/ml or 300 mcg/ml.
- **Inactive ingredients:** Glycine I.P. 30 mg, Sodium Chloride I.P. 5.84 mg, Water for Injection I.P. q.s. to 1.0 ml.

10. Details of manufacturer:
BHARAT SERUMS AND VACCINES LIMITED
Plot No. K-27, K-27 Part and K-27/1, Anand Nagar, Jambivili Village, Additional MIDC, Ambernath (East), Thane 421506, Maharashtra State, India.

11. Details of permission or license number with date:
KD-4.

12. Date of revision:
Version: 04.
Dated: 28th October 2024.