Prescribing Information for TGlobulin25®

TGlobulin25®

Rabbit antithymocyte immunoglobulin

Pharmaceutical form:

Each vial contains sterile lyophilized powder for preparation of solution for intravenous infusion.

Compounds:

Each vial of TGlobulin25 contains 5 mg/ml of rabbit anti human thymocyte globulin, which after dissolving in 5 ml of sterile WFI (water for injection), will contain 25 mg of the active pharmaceutical ingredient.

Auxiliary substances:

Mannitol, glycine and sodium chloride.

Clinical usage and dosage:

Determining the dose and the type of prescription is according to the standard references and with the physician's prescription and depends on its combination with other immune suppressive medications. However, the following doses can be recommended:

1- Immune suppression in transplantation:

1-1- Prevention of acute kidney transplant rejection:

Daily 1.5 mg of TGlobulin25 per kilogram of the patient's weight (per KG) for 4 to 7 days so that the first dose is prescribed prior to reperfusion of the donor kidney) be done.

1-2- Treatment of acute kidney transplant rejection:

Daily 1.5 mg of TGlobulin25 per KG (kilogram of the patient's weight) for 7 to 14 days.

Prescribed dose adjustments:

In case of side effects, the drug dosage may need to be adjusted by specialized physician. The number of blood cells and platelets should be monitored during and after receiving TGlobulin25.

• If the number of peripheral platelets is between 50,000 to 75,000 cells/mm^3 or the number of white blood cells (WBC) is between 2,000 to 3,000 cells/mm^3, the prescribed dose of TGlobulin25 should be reduced to half.

• In severe thrombocytopenia (less than 50,000 cells/mm^3) or severe leukopenia (less than 2,000 cells/mm^3), treatment with TGlobulin25 should be stopped.

Method of drug preparation and administration:

- After calculating the number of TGlobulin25 vials required for the patient, take the vials out of the refrigerator to reach the ambient temperature.
- Following aseptic principles, remove the cap of the vials to reveal the rubber cap. Disinfect the caps of the vials using 70% alcohol.
- Dissolve the contents of each vial of TGlobulin25 with 5 ml of distilled water for injection (sterile, non-pyrogenic) and completely by swirling. Check the vial to ensure complete dissolution of the lyophilized powder and continue swirling the vial until all the powder is completely dissolved. If any powder remains undissolved, discard the vial. After dissolving the drug, a clear to slightly milky solution without sediment or

particles should be created. This solution should be used immediately after preparation.

- Transfer the dissolved contents of TGlobulin25 vials to the infusion bag (0.9% sodium chloride injection or 5% dextrose injection). The recommended volume for infusion is 50 ml for every 5 mg of TGlobulin25 (one vial). The usual total volume of each infusion is 50 to 500 ml. In order to properly mix the infusion solution, gently invert the infusion bag once or at most twice.

• TGlobulin25 infusion should be done under strict medical supervision and in the hospital, and during the infusion, the patient's clinical symptoms should be carefully monitored.

• Administering corticosteroids, acetaminophen with or without antihistamine, one hour before the start of the infusion of each dose of TGlobulin25 is recommended to reduce the incidence and severity of infusion-related reactions.

• TGlobulin25 infusion should be done slowly and through the central vein (CV line) using a serum set with a 0.22 micron filter, so that the first injection lasts at least 6 hours and the subsequent doses last at least 4 hours.

• If, according to the physician's recommendation, infusion through the central vein is not possible, the infusion of TGlobulin25 through a peripheral vein with high blood flow (high-flow vein) should be combined with an anticoagulant (such as heparin, for example 1000 units). And corticosteroid (such as hydrocortisone, for example 20 mg) should be injected in an infusion bag containing 500 ml of 0.9%. sodium chloride solution. The first two doses should be infused over 6 hours, and the third doses should be infused over 4 hours (Reference: **UpToDate**).

Simultaneous administration with other drugs:

• TGlobulin25 is generally prescribed in a combined treatment along with several other immunosuppressive drugs.

• Due to immunosuppression in the transplant regimen, the patient should be carefully monitored for various bacterial, viral, and fungal infections, and receive prophylaxis or related treatment as prescribed by physician.

• If the patient or kidney donor is seropositive for Cytomegalovirus (CMV), prophylaxis with antiviral drugs is recommended.

Prohibited usage:

• Acute infections

• Thrombocytopenia less than 50,000 cells/mm^3 or leukopenia less than 2,000 cells/mm^3.

• Known sensitivity to rabbit proteins or any of the components of this medicinal product.

Warnings and special recommendations for usage:

• During the administration of TGlobulin 25, the doctor may reduce the prescribed dose of other immunosuppressive drugs.

• The prescribed dose of TGlobulin25 is different from the prescribed dose of other similar types of antithymocyte globulin drugs, and the doctor must ensure that the prescribed dose of TGlobulin25 is in accordance with the standards of rabbit antithymocyte immunoglobulin administration recommended here or by physician based on clinical trial and PMS results.

• If an anaphylactic reaction is observed, the injection should be stopped immediately, and the emergency measures required for this condition should be carried out.
Some severe side effects during drug administration, including cytokine release syndrome, are related to the speed of injection. Therefore, all the requirements and recommendations mentioned in the "**Method of drug preparation and administration**" section must be followed. Pretreatment with corticosteroids and antihistamines, reducing the amount of injection and using more sterile isotonic solution (0.9% sodium chloride or 5% dextrose injection) can reduce the severity of these reactions.
• The safety of simultaneous administration of live attenuated vaccines with rabbit antithymocyte immunoglobulin has not been investigated. Therefore, it is not recommended to receive live attenuated viral vaccines in patients who have recently received TGlobulin 25.

Pregnancy and breastfeeding:
No study has been conducted to check the safety of rabbit antithymocyte immunoglobulin during pregnancy and breastfeeding. This medicine should not be used during pregnancy and in very necessary cases, a decision should be made according to the opinion of a specialized physician after weighing the benefits against the harms of the medicine.
It is not known whether this drug enters human milk, but considering that other immunoglobulins can enter human milk, breastfeeding should be stopped when using TGlobulin25.

Adverse effects and side effects:
• Very common side effects (with a prevalence of more than 5%) reported after taking TGlobulin25, including urinary tract infection, abdominal pain, increased blood pressure, nausea, shortness of breath, fever, headache, anxiety, chills, increased potassium levels. Blood is the reduction of white blood cells and platelets in the blood.
• Local reactions at the infusion site such as pain, swelling and redness of the skin may occur.
• Adverse reactions caused by excessive immunosupresion such as infections (bacterial, fungal, viral and parasitic) and rare neoplastic malignancies (especially lymphoproliferative syndrome) during treatment with rabbit antithymocyte immunoglobulin, which can lead to the risk of death have been reported.

Overprescribing:
Excessive administration of TGlobulin25 can cause leukopenia and thrombocytopenia, which can be controlled by adjusting the dose. In case of overdose, TGlobulin25 administration should be stopped, and the amount of other immunosuppressive drugs should be re-adjusted based on the amount of leukocytes and lymphocytes in the peripheral blood. If necessary, plasmapheresis therapy can be used to reduce the serum concentration of TGlobulin25.

Pharmaceutical specifications:
Selective immunosuppressive agents
ATC code: L04AA04
Anti-Thymocyte Immunoglobulin

1-Pharmacodynamic characteristics:

Rabbit antithymocyte immunoglobulin is a polyclonal immunosuppressant antibody with an effect on human T lymphocytes. The mechanism of action of antithymocyte rabbit immunoglobulin is not fully understood but may involve removal of T lymphocytes from the circulation, regulation of their activation, homing, and cell lethality.

Rabbit antithymocyte immunoglobulin contains antibodies against different T lymphocytes markers, including CD2, CD3, CD4, CD8, CD11a, CD18, CD25, CD44, CD45, HLA-DR, HLA Class I heavy chains, and β2 microglobulin. Antithymocyte globulin inhibits the proliferative responses of T lymphocytes to mitogens in laboratory conditions at a concentration of more than 0.1 mg/ml.

Elimination of T lymphocytes is usually observed one day after the start of treatment. The effectiveness of administration of antithymocyte globulin in transplant rejection caused by humoral immunity (mediated by antibodies) has not been observed.

2-Pharmacokinetic characteristics:

4-8 hours after an infusion of 1.25-1.5 mg/kg/day (over a period of 4-11 days), the average serum level of rabbit antithymocyte immunoglobulin is about 10-40 µg/ml after the first infusion and 23-170 µg /ml is reached after the last iinfusion, which is eliminated with a serum half-life of about 2 to 3 days. Rabbit immunoglobulin can be detected in most patients up to two months after injection.

Significant immunity against rabbit immunoglobulin is observed in some patients. In most cases, this process occurs in the first 15 days after starting the treatment. The drug level decreases more rapidly in patients with this reaction.

Preclinical safety studies:

Regarding TGlobulin25, no significant toxicity has been observed in animal studies.

Clinical trial studies:

So far, two clinical studies have been conducted for TGlobulin25.

1-Investigating the effectiveness and safety of TGlobulin25 for inducing immunosuppression therapy in adults with kidney transplant compared to Thymoglobulin® from Sanofi:

For safety outcomes including reduction in mortality, CMV infection, adverse events, and serious adverse events and for efficacy outcomes including graft rejection, graft survival rate, and delayed graft function (DGF), there was no statistically significant differences observed between safety and the effectiveness of TGlobulin25 and Thymoglobulin® as the brand drug and they were similar in terms of safety and effectiveness during the follow-up period of the study.

2-Investigating the incidence of thromboembolic events in TGlobulin25 recipients compared to Thymoglobulin®:

During the one month follow-up after transplantation, there was no statistically significant difference between the recipients of TGlobulin25 and Thymoglobulin® in terms of thromboembolic events, transplant rejection, DGF, nephrectomy and death.

In this study, it was found that in terms of dosing, there should be no difference between the two types of antithymocyte rabbit immunoglobulins.

Also, in this study, it was found that not adding heparin to the rabbit antithymocyte immunoglobulin infusion bag (if administered from a peripheral vein) may lead to an increase in the incidence of thromboembolic events. Therefore, the treatment staff should observe the use of anticoagulants [according to the recommendation stated in the "method of drug preparation and administration" section above].

Drug interactions:

The study of drug interactions in the case of TGlobulin25 has not been done. This medicine should not be combined with other substances and medicines. The use of injectable isotonic solutions (sterile, non-pyrogenic) of 0.9% sodium chloride or 5% dextrose for dilution and preparation of medicinal infusion solution is allowed.

TGlobulin25 can cause antibodies that cross-react with rabbit immunoglobulins.

Storage considerations:

The medicine should be kept away from light and in a refrigerator (2 to 8 degrees Celsius). **Avoid freezing of the medicine.**

The drug should be used immediately after dissolution (especially after dilution for infusion).

The storage or consumption of unprescribed or leftover solution or expired medicine should be avoided.

Drug packaging:

The drug powder is in a transparent glass vial of 10 ml with a rubber stopper (Chlorobutyl) in a box.

References:

1- Uptodate 2022

2- Thymoglobulin® Prescribing information revised 03.2023

Manufacturer Information:

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