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

This package insert is continually updated. Please read carefully before using a new pack.

Anti-human Thymocyte Immunoglobulin (Rabbit) E.P.

Thymoglobuline® 5mg/ml

Powder for concentrate for solution for infusion

COMPOSITION
After reconstitution with 5ml Water for Injection (WFI) I.P., the solution contains 5mg rabbit anti-human thymocyte immunoglobulin/ ml (concentrate)
Corresponding to 25mg/5ml of rabbit anti-human thymocyte immunoglobulin per vial.

PHARMACEUTICAL FORM
Powder for concentrate for solution for infusion.

INDICATIONS
- Immunosuppression in transplantation: prophylaxis and treatment of graft rejection.
- Prophylaxis of acute and chronic graft versus host disease, after haematopoietic stem cell transplantation.
- Treatment of steroid-resistant, acute graft versus host disease (GvHD).
- Haematology: treatment of aplastic anemia.

DOSAGE AND ADMINISTRATION
Posology
The posology depends on the indication, the administration regimen and possible association of combination with other immunosuppressive agents. The following dosage recommendations may be used as a reference. Treatment can be discontinued without gradual tapering of the dose.

– Immunosuppression in transplantation:
• Prophylaxis of acute graft rejection: 1 to 1.5 mg/kg/day for 2 to 9 days after transplantation of a kidney, pancreas or liver and for 2 to 5 days after heart transplantation, corresponding to a cumulative dose of 2 to 7.5 mg/kg in heart transplantation and 2 to 13.5 mg/kg for other organs.
• Treatment of acute graft rejection: 1.5 mg/kg/day for 3 to 14 days, corresponding to a cumulative dose of 4.5 to 21 mg/kg.

– Prophylaxis of acute and chronic graft versus host disease:
In transplantation of grafts (bone marrow or haematopoietic stem cells from peripheral blood) from related non-HLA-identical donors or from unrelated HLA-identical donors, it is recommended in adult patients that Thymoglobuline® be administered, as a preliminary therapy, at a dose of 2.5 mg/kg/day from day -4 to day -2 or -1, corresponding to a cumulative dose of 7.5 to 10 mg/kg.

– Treatment of steroid-resistant, acute graft versus host disease:
The dosage must be determined on an individual basis. It is usually between 2 and 5 mg/kg/day for 5 days.

– Treatment of Aplastic anemia:
2.5 to 3.5 mg/kg/day for 5 consecutive days or a cumulative dose of 12.5 to 17.5 mg/kg The indication for aplastic anemia has not been established by controlled clinical trials carried out with this medicinal product.

Method of administration
Rabbit anti-human thymocyte immunoglobulin is usually administered in the context of a therapeutic regimen combining several immunosuppressive agents. It is recommended to administer pre-medication with intravenous corticosteroids and antihistamines prior to infusion of rabbit anti-human thymocyte immunoglobulin. Anti pyretic agents (e.g. paracetamol) may also increase the tolerability of the initial infusion. Infuse slowly into a high -flow vein. Adjust the infusion rate so that the total duration of infusion is not less than 6 hours. See section Warnings and section adverse reactions for advice about the management of any adverse events associated with infusion

CONTRAINDICATIONS
Thymoglobuline® is contraindicated in patients with:

- Hypersensitivity to rabbit proteins or to any product excipients
- Active acute or chronic infections, which would contraindicate any additional immunosuppression

WARNINGS
Immune-mediated reactions
In rare instances, serious immune-mediated reactions have been reported with the use of Thymoglobuline® and consist of anaphylaxis or severe cytokine release syndrome (CRS).
Very rarely, fatal anaphylaxis has been reported (See Adverse reactions). If an anaphylactic reaction occurs, the infusion should be terminated immediately, and appropriate emergency treatment should be initiated. Any further administration of Thymoglobuline® to a patient who has a history of anaphylaxis to Thymoglobuline® should be undertaken only after serious consideration.
Severe, acute infusion-associated reactions (IARs) are consistent with CRS attributed to the release of cytokines by activated monocytes and lymphocytes. In rare instances, these reported reactions are associated with serious cardiorespiratory events and/or death (See Precautions and Adverse reactions).

Infection
Thymoglobuline® is routinely used in combination with other immunosuppressive agents. Infections (bacterial, fungal, viral, and protozoal), reactivation of infection (particularly cytomegalovirus [CMV]), and sepsis have been reported after Thymoglobuline® administration in combination with multiple immunosuppressive agents. In rare cases, these infections have been fatal.

PRECAUTIONS
General
Appropriate dosing for Thymoglobuline® is different from dosing for other anti-thymocyte globulin (ATG) products, as protein composition and concentrations vary depending on the source of ATG used.
Physicians should therefore exercise care to ensure that the dose prescribed is appropriate for the ATG product being administered.

Thymoglobuline® should be used under strict medical supervision in a hospital setting, and patients should be carefully monitored during the infusions. IARs may occur following the administration of Thymoglobuline® and may occur as soon as the first or second infusion during a single course of Thymoglobuline® treatment.

Close compliance with the recommended dosage and infusion time may reduce the incidence and severity of IARs. Additionally, reducing the infusion rate may minimize many of these IARs. Premedication with antipyretics, corticosteroids, and/or antihistamines may decrease both the incidence and severity of these adverse reactions.

Rapid infusion rates have been associated with case reports consistent with CRS. In rare instances, severe CRS can be fatal.

Hematologic Effects

Thrombocytopenia and/or leukopenia (including lymphopenia and neutropenia) have been identified and are reversible following dose adjustments. When thrombocytopenia and/or leukopenia are not part of the underlying disease or associated with the condition for which Thymoglobuline® is being administered, the following dose reductions are suggested:

- A reduction in dosage must be considered if the platelet count is between 50,000 and 75,000 cells/mm^3 or if the white blood cell count is between 2,000 and 3,000 cells/mm^3;
- Stopping Thymoglobuline® treatment should be considered if persistent and severe thrombocytopenia (<50,000 cells/mm^3) occurs or leukopenia (< 2,000 cells/mm^3) develops.

White blood cell and platelet counts should be monitored during and after Thymoglobuline® therapy.

Infection

Infections, reactivation of infection, and sepsis have been reported after Thymoglobuline® administration in combination with multiple immunosuppressive agents. Careful patient monitoring and appropriate anti-infective prophylaxis are recommended.

Malignancy

Use of immunosuppressive agents, including Thymoglobuline®, may increase the incidence of malignancies, including lymphoma or lymphoproliferative disorders (which may be virally mediated). These events have sometimes been associated with fatal outcome (See Adverse Reactions).

Special Considerations for Thymoglobuline® Infusion

As with any infusion, reactions at the infusion site can occur and may include pain, swelling, and erythema.

The recommended route of administration for Thymoglobuline® is intravenous infusion using a high flow vein; however, it may be administered through a peripheral vein. When Thymoglobuline® is administered through a peripheral vein, concomitant use of heparin and hydrocortisone in an infusion solution of 0.9% sodium chloride may minimize the potential for superficial thrombophlebitis and deep vein thrombosis. The combination of Thymoglobuline®, heparin, and

hydrocortisone in a dextrose infusion solution has been noted to precipitate and is not recommended (See Incompatibilities)

Immunizations
The safety of immunization with attenuated live vaccines following Thymoglobuline® therapy has not been studied; therefore, immunization with attenuated live vaccines is not recommended for patients who have recently received Thymoglobuline®.

INTERACTIONS
No drug interaction studies have been performed.

PREGNANCY
Animal reproduction studies have not been conducted with Thymoglobuline®. It is not known whether Thymoglobuline® can cause fetal harm or affect reproduction capacity. Thymoglobuline® should be given to a pregnant woman only if clearly needed.

Thymoglobuline® has not been studied in labor or delivery.

LACTATION
Thymoglobuline® has not been studied in nursing women. It is not known whether this drug is excreted in human milk. Because other immunoglobulins are excreted in human milk, breast feeding should be discontinued during Thymoglobuline® therapy.

DRIVING A VEHICLE OR PERFORMING OTHER HAZARDOUS TASKS
Given the possible adverse events that can occur during the period of Thymoglobuline® infusion, in particular CRS, it is recommended that patients should not drive or operate machinery during the course of Thymoglobuline® therapy.

ADVERSE REACTIONS
The following CIOMS frequency rating is used, when applicable:
Very common ≥ 10%; Common ≥1 and ≤ 10%; Uncommon ≥ 0.1 and ≤ 1%;
Rare ≥ 0.01 and ≤ 0.1%; Very rare ≤ 0.01%; Not known (cannot be estimated from available data).

Infections and infestations
- **Infection** (including reactivation of infection)
- **Sepsis**

(See WARNINGS and PRECAUTIONS – Immune-mediated reactions)

Neoplasms benign, malignant and unspecified (incl cysts and polyps)
- **Lymphoproliferative disorder**
- **Lymphomas** (which may be virally mediated)
- **Neoplasms malignant (**Solid tumors)

(See PRECAUTIONS – Malignancy)

Blood and lymphatic system disorders
- **Febrile neutropenia**
- **Disseminated intravascular coagulopathy**

- **Coagulopathy**

Immune System disorders

- **Cytokine release syndrome (CRS) -** Post-marketing reports of severe CRS have been associated with cardiorespiratory dysfunction (including hypotension, acute respiratory distress syndrome [ARDS], pulmonary edema, myocardial infarction, tachycardia, and/or death). (See WARNINGS)
- **Anaphylactic reaction** (See WARNINGS)
- **Serum Sickness** (including reactions such as fever, rash, urticaria, arthralgia, and/or myalgia). Serum sickness tends to occur 5 to 15 days after onset of Thymoglobuline® therapy. Symptoms are usually self-limited or resolve rapidly with corticosteroid treatment.

Hepatobiliary disorders

- **Transaminases increased-**Transient reversible elevations in transaminases without any clinical signs or symptoms have also been reported during Thymoglobuline® administration.
- **Hepatocellular injury**
- **Hepatotoxicity**
- **Hepatic Failure** (cases have been reported secondary to allergic hepatitis and reactivation of hepatitis in patients with hematologic disease and/or stem cell transplant as confounding factors).

General disorders and administration site conditions

- **Infusion related reactions (**Infusion associated Reactions (IARs)

Clinical manifestations of IARs have included some of the following signs and symptoms: fever, chills/rigors, dyspnea, nausea/vomiting, diarrhea, hypotension or hypertension, malaise, rash, urticaria, decreased oxygen saturation, and/or headache. (See PRECAUTIONS)

OVERDOSE

Inadvertent overdose may induce leukopenia (including lymphopenia and neutropenia) and thrombocytopenia.

INTERFERENCE WITH LABORATORY AND DIAGNOSTIC TESTS

Thymoglobuline® has not been shown to interfere with any routine clinical laboratory tests that use immunoglobulins. However, Thymoglobuline® may interfere with rabbit antibody-based immunoassays and with crossmatch or panel-reactive antibody cytotoxicity assays, in particular.

ABUSE AND DEPENDENCE

Not applicable

PHARMACEUTICAL PARTICULARS

List of excipients

– Glycine
– sodium chloride
– Mannitol.

Other components:
Thymoglobuline® may also contain residues of polysorbate, from the manufacturing process.

Incompatibilities
Based on a single compatibility study, the combination of Thymoglobuline®, heparin, and hydrocortisone in a dextrose infusion solution has been noted to precipitate and is not recommended. In the absence of additional pharmaceutical incompatibility data, Thymoglobuline® should not be mixed with other medicinal products in the same infusion.

Shelf life
36 months
Immediate use after dilution is recommended in order to prevent microbial contamination.
If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2°C to 8°C, unless reconstitution or dilution has taken place in controlled and validated aseptic conditions.

Special precautions for storage
Store and transport refrigerated (at 2°C to 8°C).
Do not freeze.
During transport a temperature excursion up to 25°C for 3 days will not alter the medicinal product characteristics.
For storage conditions of the reconstituted and diluted medicinal product, see section Shelf life.

Nature and contents of outer packaging
Powder in a vial (type I glass) with a stopper (chlorobutyl). Each pack contains one 10 ml vial

Instructions for use and handling
Reconstitute the powder using 5 ml of sterile water for injection to obtain a solution containing 5mg protein per ml.
The solution is clear or slightly opalescent. Reconstituted product should be inspected visually for particulate matter and discoloration. Should some particulate matter remain, continue to gently rotate the vial until no particulate matter is visible. If particulate matter persists, discard the vial. Immediate use of reconstituted product is recommended.
Each vial is for single use only. Depending on the daily dose, the reconstitution of several vials of Thymoglobuline® powder might be needed. Determine the number of vials to be used and round up to the nearest vial. To avoid inadvertent administration of particulate matter from reconstitution, it is recommended to use a 0.22 µm in-line filter.

The daily dose is diluted in an infusion solution (0.9 % sodium chloride or 5% glucose solution) so as to obtain a total infusion volume of 50 to 500 ml (usually 50 ml/vial).
The medicinal product should be administered on the same day.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

MANUFACTURED BY:
Fill/Finish, labeling, packaging and batch release site:
Genzyme Ireland Ltd, IDA Industrial Park, Old Kilmeaden Road, Waterford, Ireland.

QC testing site: Sanofi Winthrop Industrie, 23 boulevard Chambaud de la Bruyère, 69007 Lyon, France.

Importer:
Sanofi Healthcare India Private Limited, Citylink Warehousing Complex, Bldg. No. B1, Gala No. 4, S No.121/10/A,121/10/B & 69, NH3, Village Vadpe, Tal: Bhiwandi-16, Thane Z5- 421302, Maharashtra.

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Source: 1) CCDS version no. 2 dated 16 July 2015.
2) UK Summary of Product characteristics dated 13th November 2020