

PACKAGE LEAFLET: INFORMATION FOR THE USER

# Thymoglobuline® 5 mg/ml

Rabbit anti-human thymocyte immunoglobulin

**powder for solution for infusion**

**sanofi**

**Read all of this leaflet carefully before you start using this medicine because it contains important information for you.**

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

**What is in this leaflet**

1. What Thymoglobuline is and what it is used for
2. What you need to know before you use Thymoglobuline
3. How to use Thymoglobuline
4. Possible side effects
5. How to store Thymoglobuline
6. Contents of the pack and other information

**1. WHAT THYMOGLOBULINE IS AND WHAT IT IS USED FOR**

Pharmacotherapeutic group: selective immunosuppressants.

**Thymoglobuline** is available as lyophilized powder for solution to be diluted for infusion (25 mg. Box of 1).

**Thymoglobuline** is an anti-human thymocyte immunoglobulin made from rabbit blood into which cells from the human thymus have been injected. It belongs to a group of medicines called immunosuppressants (anti-rejection medicines).

It is used for:

- Immunosuppression in transplantation: prevention and treatment of graft rejection. It is a type of medicine known as an immunosuppressant (anti-rejection medicine). When a patient receives an organ, the body's natural defense system tries to reject it. **Thymoglobuline** changes the body's defense mechanism and helps it accept the transplanted organ.
- Prevention of acute and chronic graft-versus-host disease (a disease in which the functional immune cells in the transplanted bone marrow recognize the recipient as “foreign” and mount an immune attack) in hematopoietic stem cell transplantation (transplantation of cells capable of forming blood cells).
- Treatment of steroid-resistant acute graft-versus-host disease.
- In hematology: treatment of bone marrow depression. Bone marrow depression is a rare type of blood disorder in which the body does not make enough blood cells.

**2. WHAT YOU NEED TO KNOW BEFORE YOU USE THYMOGLOBULINE**

**Contraindications**  
**Do not use Thymoglobuline:**

- If you are allergic to rabbit proteins or any of the other ingredients of this medicine (listed in section 6).
- If you have an acute or chronic infection that would prevent further immunosuppression (as **Thymoglobuline** decreases your body's ability to fight infections).

**Warnings and precautions**  
Talk to your doctor, pharmacist or nurse before using **Thymoglobuline**.

**Thymoglobuline** should always be used under strict medical surveillance in a hospital setting. During treatment with Thymoglobuline, your doctor will perform regular blood tests and other tests to monitor your health. Due to the way this medicine works, it might affect your blood and other organs.

Tell your doctor if you have ever had an allergic reaction to animals or other medicines. The doctor will closely monitor you and stop treatment if there are any signs of an allergic reaction to **Thymoglobuline**.

Some severe side effects may be associated with the infusion rate. Patients should be carefully monitored during the infusion.

If undesirable reactions occur, either the infusion rate can be reduced or the infusion can be stopped until the symptoms disappear.

Administration should be stopped immediately and permanently if a generalized allergic reaction occurs. If shock occurs (suddenly feeling ill and a drop in blood pressure), symptomatic treatment should be instituted for the state of shock.

Tell your doctor if you have a blood disorder, such as thrombocytopenia (a lower than normal number of platelets in the blood) or leukopenia (a lower than normal number of white blood cells). Your dose will depend on the number of white blood cells or platelets present in your blood, which will be checked before, during and after treatment.

**Thymoglobuline** is often used in combination with other immunosuppressant medicines.

Infections, reactivation of infections and sepsis (infection in the blood that spreads throughout the entire body) and febrile neutropenia (fever associated with a lower than normal number of certain white blood cells) have been reported after taking these medicines in combination.

In bone marrow depression, immunosuppressant treatment contributes to the risk of infection (in particular fungal infection) associated with the bone marrow depression itself.

Use of immunosuppressant medicines, including **Thymoglobuline**, may increase the risk of developing cancer, especially lymphoma or lymphoproliferative syndrome (involving an abnormal increase in the number of white blood cells).

The safety of immunization with live attenuated (weakened, less virulent) vaccines after treatment with **Thymoglobuline** has not been studied; immunization with live attenuated vaccines is therefore not recommended in patients who recently received **Thymoglobuline** (see also “Other medicines and **Thymoglobuline**”).

Components of human origin (red blood cells treated with formaldehyde and thymic cells) are used in the **Thymoglobuline** manufacturing process. When medicines are made from human blood or plasma, certain measures are implemented to prevent the transmission of infections to patients. These measures include thorough screening of blood and plasma donors to ensure that people who may be carriers of infections are ruled out, as well as examination of each donation and of plasma from multiple donors for signs of viruses or infections. Manufacturers of these products also include phases to inactivate or remove viruses when treating blood or plasma. Despite these measures, when medicines prepared from human blood components are administered, the possibility of transmitting an infection cannot be totally ruled out. This risk also applies to unknown or emerging viruses and other types of infection.



The measures taken are considered effective for enveloped viruses such as the human immunodeficiency virus (HIV), hepatitis B virus, hepatitis C virus and the non-enveloped HAV virus.

The measures taken may be of limited efficacy against non-enveloped viruses such as parvovirus B19. Parvovirus B19 infection can be serious in pregnant women (fetal infection) and in people with suppressed immune systems and certain types of anemia.

**Other medicines and Thymoglobuline**  
Tell your doctor, pharmacist or nurse if you are taking, have recently taken or may take any other medicines.

The use of immunosuppressants (ciclosporin, tacrolimus or mycophenolate mofetil) carries a risk of excessive immunosuppression, which may lead to lymphoproliferation (abnormal increase in the number of white blood cells). Your doctor will therefore need to know whether you are using these medicines.

Do not get vaccinated during or shortly after treatment with **Thymoglobuline** without first discussing it with your doctor, as this might cause side effects (if it is a live vaccine) or might not work due to a lack of immune system response.

**Pregnancy and breast-feeding**  
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor, pharmacist or nurse for advice before using this medicine.

**Pregnancy**  
Due to a lack of data, **Thymoglobuline** may only be given to pregnant women if it is absolutely necessary.

**Breast-feeding**  
Do not breast-feed if you are using **Thymoglobuline**, as the medicine might pass into the breast milk and affect the baby.

**Driving and using machines**  
As **Thymoglobuline** may make you feel sick, tired or dizzy, you should not drive or use tools or machines.

**Thymoglobuline contains sodium**  
This medicine contains 4 mg of sodium (main component of cooking salt/table salt) per bottle. This is equivalent to 0.2% of the recommended maximum daily intake of sodium for an adult.

**3. HOW TO USE THYMOGLOBULINE**

Your medicine will be given to you by a doctor or nurse in a hospital. **Thymoglobuline** is administered through a plastic tube (a catheter) directly into your bloodstream (intravenous infusion) over a period of at least 4 hours. The first dose may be given over a longer period of time.

The dose given to you will vary depending on your weight, the medical problem being treated and other medicines you are receiving at the same time.

- Immunosuppression in transplantation:
  - o Prevention of acute graft rejection:  
Between 1 and 1.5 mg per kilogram, every day for 2 to 9 days after a kidney, pancreas or liver transplant and for 2 to 5 days after a heart transplant, i.e. a total dose of 2 to 7.5 mg/kg in heart transplantation and 2 to 13.5 mg/kg for other organs.
  - o Treatment of acute graft rejection:  
1.5 mg per kilogram, every day for 3 to 14 days, i.e. a total dose of 4.5 to 21 mg/kg.
- Prevention of acute and chronic graft-versus-host disease:  
In graft transplants (bone marrow or peripheral blood hematopoietic stem cells) from non-HLA-identical related donors or HLA-identical unrelated donors, for adult patients, it is recommended that **Thymoglobuline** be administered as pre-treatment at a dose of 2.5 mg per kilogram, every day from day -4 to day -2 or -1, i.e. a total dose of 7.5 to 10 mg/kg.
- Treatment of acute steroid-resistant graft-versus-host disease:  
The dosage must be determined on a case-by-case basis. It is usually between 2 and 5 mg per kilogram, every day for 5 days.
- Bone marrow depression:  
Between 2.5 and 3.5 mg per kilogram, every day for 5 days in a row, i.e. a total dose of 12.5 to 17.5 mg/kg.  
The indication for bone marrow depression has not been established through controlled clinical trials with this medicine.

Your doctor or nurse will check your condition regularly while you are being given your first dose, as this is the time when you are most likely to experience side effects. They will check for any rashes and monitor your pulse, blood pressure and breathing. From time to time, your doctor will also arrange for you to have a blood test to monitor the number of white blood cells.

If your white blood count is low, your doctor may also give you medicines to prevent or treat infections; if your platelet count is low, your doctor may give you a platelet transfusion.

The dose of **Thymoglobuline** may be changed by your doctor if you have side effects.

**If you receive more Thymoglobuline than you should**  
You are unlikely to be given more **Thymoglobuline** than you should be given, as you will be closely monitored by your doctor or nurse during your treatment. If this were to happen, you might develop thrombocytopenia (a lower than normal number of platelets) or leukopenia (a lower than normal number of white blood cells). This means that you may experience fever, chills, sore throat and mouth ulcers and that you will be more prone to bleeding and bruising than normal.

**If you forget to use Thymoglobuline**  
Do not use a double dose to make up for a forgotten dose.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

**4. POSSIBLE SIDE EFFECTS**

Like all medicines, this medicine can cause side effects, although not everybody gets them. Some side effects, such as fever, rash and headache, or other effects affecting pulse, blood pressure and breathing, as well as some allergic reactions, are more likely to occur with your first or second dose of **Thymoglobuline** than with subsequent doses.

Tell your doctor immediately if you have:

- an itchy skin rash,
- difficulty breathing,
- stomach pain,
- swelling of the face, mouth or throat.

These are signs of an allergic reaction that could be life-threatening.

Sometimes, infusion with **Thymoglobuline** may cause the following additional side effects.  
Tell your doctor as soon as possible if you notice any of these effects:

- difficulty breathing, wheezing or cough,
- feeling sick or vomiting,
- dizziness or generally feeling ill,
- joint pain,
- headache,
- bleeding or bruising more frequently than usual,
- irregular or rapid heartbeat,
- symptoms of an infection such as fever, chills, sore throat, mouth ulcers.

During and after treatment with **Thymoglobuline**, some patients have experienced a temporary increase in certain liver function test values (laboratory tests indicating how your liver is working). In general, there are no symptoms and these liver function values return to normal without treatment.

The side effects listed below were observed during an observational study. Not all of them were necessarily caused by **Thymoglobuline**. Very common side effects (which may affect more than 1 in 10 people) include:

- low number of white blood cells; low number of platelets,
- low number of red blood cells (anemia),
- fever,
- infection.

Common side effects (which may affect up to 1 in 10 people) include:

- diarrhea, difficulty swallowing, nausea, vomiting,
- chills,
- serum sickness, a disease caused by antibodies against Thymoglobuline, causing skin rashes, hives (red, itchy marks), joint pain, kidney problems and swollen lymph nodes, developing within 5 to 15 days. Serum sickness is usually mild and disappears without treatment or with steroids within a short period of time,
- increase in certain liver enzymes in your blood,
- muscle pain,
- malignant tumors,
- shortness of breath,
- itching, skin rash,
- low blood pressure.

Uncommon side effects (which may affect more than 1 in 1 000 people):

- liver disease (liver failure).

Side effects of unknown frequency (cannot be estimated from the available data):

- Increase in the level of bilirubin in the blood (increase in the laboratory parameter).

These side effects may be mild and disappear with treatment. They can also be reduced by changing the **Thymoglobuline** dose or by lengthening the time over which it is given.

Side effects sometimes occur several months after treatment. In patients using **Thymoglobuline** with other immunosuppressants, delayed effects may occur, including an increased risk of infections and certain types of cancer.

Infections, reactivation of infections, febrile neutropenia and sepsis have been reported after administration of **Thymoglobuline** in combination with several immunosuppressants. In rare cases, malignant tumors, including but not limited to lymphoproliferative syndromes and other lymphomas, as well as solid tumors, have been reported. These events have sometimes been fatal. These adverse events have always been associated with a combination of several immunosuppressants.

If you are given **Thymoglobuline** with other medicines that suppress your immune system, you may be prone to infections, blood or otherwise.

**Reporting of side effects**  
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet.

By reporting side effects you can help provide more information on the safety of this medicine.

**5. HOW TO STORE THYMOGLOBULINE**

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the packaging. Store in a refrigerator (2°C – 8°C).

**Do not freeze.**

**Thymoglobuline** must not be used if particles in the vial do not disappear when the vial is shaken.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

**6. CONTENTS OF THE PACK AND OTHER INFORMATION**

**What Thymoglobuline 5 mg/mL powder for solution for infusion contains**

- The active substance is: Rabbit anti-human thymocyte immunoglobulin...5 mg/mL after reconstitution, i.e. 25 mg in a vial.
- The other ingredients are: mannitol, glycine, sodium chloride (salt).

**What Thymoglobuline 5 mg/mL powder for solution for infusion looks like and contents of the pack**  
**Thymoglobuline** 5 mg/mL powder for solution for infusion is available as a powder for solution to be diluted for infusion (in a (25 mg) vial, box of 1).

**Thymoglobuline** 5 mg/mL powder for solution for infusion is supplied in a glass vial containing creamy white powder. Before use, this powder is dissolved in 5 mL of water for injections.

Each mL of the solution obtained contains 5 mg of rabbit anti-human thymocyte immunoglobulin. The reconstituted solution is clear or slightly opalescent.

This liquid is then mixed with sodium chloride or glucose solution so that it can be administered slowly (infused) into the bloodstream.

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**The following information is intended for healthcare professionals only.**  
**Preparing the reconstituted solution and the Thymoglobuline infusion (under aseptic conditions)**  
Depending on the daily dose, calculate the number of vials to be reconstituted. Reconstitute each vial of powder with 5 mL of water for injections. In each vial, the solution obtained contains 5 mg of rabbit anti-human thymocyte immunoglobulin per mL.

Draw up the required volume of reconstituted solution from the **Thymoglobuline** vials. Add the daily dose to a solution for infusion (9 mg/mL (0.9%) sodium chloride or 5% glucose) to obtain a total infusion volume of 50 to 500 mL (usually 50 mL/vial).

The product must be administered on the same day. Use of a 0.2 micron in-line filter is recommended.  
Any unused product or waste material should be disposed of in accordance with local requirements.