ינואר 2020

רופא/ה רוקח/ת נכבד/ה,

חברת סאנופי-אוונטיס ישראל בע"מ מבקשת להודיע על עדכון **העלון לצרכן במתכונת עלון לרופא** של התכשיר:

Thymoglobuline, *powder for concentrate for solution for infusion.*

החומר פעיל:

IMMUNOGLOBULIN RABBIT ANTI-HUMAN THYMOCYTE

ההתוויה המאושרת:

Immunosuppression in transplantation: prevention and treatment of graft rejection.
Treatment of acute graft versus host disease (GvHD).
Hematology treatment of aplastic anemia.

מפורטים להלן רק תתי הסעיפים בהם נעשו העדכונים העיקריים בעלונים:

4.2 Posology and method of administration

Method of administration

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It is recommended to administer pre-medication with intravenous corticosteroids and antihistamines prior to infusion of rabbit anti-human thymocyte globulin. Anti-pyretic agents (e.g. paracetamol) may also increase the tolerability of the initial infusion.

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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 4.4 and section 4.8 for advice about the management of any adverse events associated with infusion

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4.4 Special warnings and precautions for use

Thymoglobuline should be used under strict medical supervision in a hospital setting.
Thymoglobuline must only be administered according to the instructions of a physician with experience of immunosuppressive therapy in the transplant setting. Patients should be carefully monitored during the infusion. Particular attention must be paid to monitoring the patient for any symptoms of anaphylactic shock. Close monitoring of the patient must continue during the infusion and for a period of time following the end of the infusion until the patient is stable.

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Prior to administration of Thymoglobuline it is advisable to determine whether the patient is allergic to rabbit proteins. Medical personnel and equipment, etc. must be readily at hand during the first days of therapy to provide emergency treatment if necessary.

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 section 4.8).
If an anaphylactic reaction occurs, the infusion should be terminated immediately and appropriate emergency treatment should be initiated. Equipment for emergency therapy for anaphylactic shock must be readily available.

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Hepatic diseases

Thymoglobuline has to be administered with special caution in patients with hepatic diseases as pre-existing clotting disorders may aggravate. Careful monitoring of thrombocytes and coagulation parameters is recommended.

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Precautions

General

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Thymoglobuline should be used under strict medical supervision in a hospital settingPatients should be carefully monitored during the infusion and for a period of time following the end of the infusion until the patient is stable.

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Haematological 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 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. Patients with severe neutropenic aplastic anaemia require very careful monitoring, appropriate prophylaxis and treatment of fevers and infections as well as adequate platelet transfusion support.

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

Risk of Transmission of Infectious Agents

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The measures taken for Thymoglobuline are considered effective for enveloped viruses such as HIV, HBV and HCV, and for the non-enveloped viruses such as HAV and parvovirus B19.

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Special Considerations for Thymoglobuline Infusion
As with any infusion, reactions at the injection 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.

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4.5 Interaction with other medicinal products and other forms of interaction

No drug interaction studies have been performed.

Interactions with food and drink are unlikely.

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Thymoglobuline may interfere with ELISA tests.

4.6 Fertility, pregnancy and lactation

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Breastfeeding

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Thymoglobuline has not been studied in labour or delivery.

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4.8 Undesirable effects

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Adverse reactions considered to be related to Thymoglobuline reported in clinical trials and post-marketing	
Blood and lymphatic system disorders	Very common: *anaemia*, *lymphopenia*, *neutropenia*, *thrombocytopenia* Common: *febrile neutropenia*
Gastrointestinal disorders	Common: *diarrhoea*, *dysphagia*, *nausea*, *vomiting*
General disorders and administrative site conditions	Very common: f*ever* Common: s*hivering* Uncommon: i*nfusion related reactions (infusion associated reactions (IARs)**
Hepatobiliary disorders	Common: *transaminases increased** Uncommon: *hepatocellular injury*, *hepatotoxicity*, *hepatic failure** Unknown*: Hyperbilirubinaemia*
Immune system disorders	Uncommon: *serum sickness**, *cytokine release syndrome (CRS)**, *anaphylactic reaction*
Infections and infestations	Very common: *infection (including reactivation of infection)* Common: *sepsis*
Musculoskeletal and connective tissue disorders	Common: *myalgia*
Neoplasms benign, malignant and unspecified (including cysts and polyps)	Common: *malignancy*, *lymphomas (which may be virally mediated)*, *neoplasms malignant (solid tumours)* *Uncommon: lymphoproliferative disorder*
Respiratory, thoracic and mediastinal disorders	Common: *dyspnoea*
Skin and subcutaneous tissue disorder	Common: *pruritus*, *rash*
Vascular disorder	Common: *hypotension*

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Paediatric Population
Currently available data are limited. Available information indicates that the safety profile of Thymoglobuline in paediatric patients is not fundamentally different to that seen in adults.

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5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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Lymphocyte depletion probably constitutes the primary mechanism of the immunosuppression induced by rabbit anti-human thymocyte globulin.
This depletion is both peripheral and central; peripheral lymphocyte depletion can be detected as early as 24 hours after the first infusion. Lymphocyte counts start to rise as soon as Thymoglobuline is discontinued.
This lymphocyte depletion has been shown to occur *in vitro* by a number of different mechanisms (eg apoptosis, complement dependent lysis and antibody dependent cytotoxicity); the exact mechanisms which take place *in vivo* remain undetermined.

In addition to the T cell depletion, Thymoglobuline also has effects on dendritic cells (causing apoptosis), and on B cells. *In vitro*, Thymoglobuline does not activate B-cells. Antiproliferative activity against B-cells and certain lymphoblastoid cell lines has also been demonstrated *in vitro*. This effect may be partially protective against the development of PTLD.

Thymoglobuline also has activity against a number of cell surface epitopes (e.g. CD 3, CD7, CD8, CD19, CD20, CD32, CD28), binding to them and causing downmodulation. The epitopes targeted include those involved in the immune response, in apoptosis, and in signal transduction, and include both B and T cell epitopes. In particular, Thymoglobuline has activity against both leucocyte and endothelial cell adhesion molecules (e.g. CD11a, CD18, CD11b, CD44, CD54, LPAM 1) which in animal studies has been shown to reduce tethering of leucocytes to the endothelium. Effector cells are thus unable to migrate through the endothelium to the graft. This effect may also, in theory, reduce ischaemia-reperfusion injury by allowing better flow through the microcirculation.
The combination of T cell depletion and down modulation of adhesion molecules results in interference with multiple pathways by which rejection occurs.

Paediatric population
Multiple reports regarding the use of Thymoglobuline in children have been published. These reports reflect the broad clinical experience with this product in paediatric patients and suggest that the safety and efficacy profiles in paediatric patients are not fundamentally different to that seen in adults.

However, there is no clear consensus with regards to the dosing in paediatrics. As in adults, the posology in paediatrics depends on the indication, the administration regimen, and the

combination with other immunosuppressive agents. This should be considered by physicians before deciding on the appropriate dosage in paediatrics.

5.2 Pharmacokinetic properties

Following the first infusion of 1.25 mg/kg of Thymoglobuline (in kidney transplant recipients), total serum rabbit IgG levels of between 10 and 40µg/ml are obtained. The serum levels decline steadily until the following infusion with an estimated elimination half-life of 2-3 days. There has been shown to be a relationship between dose given and total Thymoglobuline levels.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

glycine
mannitol
sodium chloride

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

השינויים המודגשים ברקע צהוב מהווים החמרה. כמו כן, בוצעו שינויים נוספים הכוללים תוספת מידע, השמטת מידע ועדכוני נוסח שאינם מהווים החמרה.

העלונים המעודכנים נשלחו לפרסום במאגר התרופות שבאתר משרד הבריאות . בנוסף ניתן לקבלם מודפסים על ידי פנייה לבעל הרישום, סאנופי-אוונטיס ישראל בע"מ, רח' בני גאון 10 נתניה או בטלפון : 09-8633700 .להלן הקישור לאתר משרד הבריאות :
https://www.old.health.gov.il/units/pharmacy/trufot/index.asp?safa=h

בברכה,

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