Package leaflet: Information for the user

Human Intravenous Immune Globulin (IVIG) 5% solution SXX HUMAN NORMAL IMMUNOGLOBULIN

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

Product Description:

Intravenous Immune Globulin (Human) 5% produced by Shanghai Xinxing Medicine Ltd Co. (IVIG 5% SXX) is a sterile solution containing 4.5%-5.5% of proteins at a low pH (4.0). The product contains 10% maltose as a stabilizer. There is no preservative used in the preparation. 98% of the proteins in the product consist of Immune Globulins out of that minimum 90% is IgG monomers. The four subclasses of IgG are present in the same ratio in the product as in normal human plasma (IgG1 60.3%-71.5%, IgG2 19.4%-31%, IgG3 5.0%-8.4%, IgG4 0.7%-4.2%). Traces of IgA and IgM are also present. IVIG 5% SXX consists of a wide range of antibodies.

Viral inactivation steps are applied to make the product more safe and free from blood borne viruses. These include "Ultra filtration and Dia-filtration", "Solvent/Detergent treatment" and "Incubation of the final product for 21 days at low pH".

Pharmacology[5, 1]:

IVIG 5% SXX is prepared from large pools of Human Plasma obtained from healthy donors (minimum 3000 donor plasma for one batch) that are screened and found negative for blood borne viruses like HBsAg, HCV and HIV. The plasma is fractionated by Cohn Oncley method and IVIG 5% SXX is obtained from Effluent III. The product contains intact and functional antibodies against antigens of various types with a wide variety. This contains various types of anti-bacterial, anti-viral and anti-fungal antibodies.

IVIG 5% SXX is used in many disease states like Primary Immunodeficiencies, Idiopathic Thrombocytopenic Purpura, Bone Marrow Transplantation and HIV Infection in children. Studies have been conducted in many other autoimmune disorders and secondary immune deficiencies. Many scientists have proposed different modes of actions for Intravenous Immune Globulins. The exact mechanism of action of IVIG 5% SXX is not yet been agreed upon but it is considered that the mode of action of immune globulin is complex, involving modulation of the expression and function of Fc receptors, interference with the activation of complement and the cytokine network, provision of antiidiotypic antibodies, and effects on the activation, differentiation and effector functions of T cells and B cells. This broad range of activities reflects the importance of immunoglobulins in the immune homeostasis in healthy people[1].

The bioavailablity of IVIG 5% SXX is 100% due to the intravenous route of administration. There is a rapid rise in the level of circulating IgG in the blood of the person receiving IVIG 5% SXX. However, due to the distribution of infused immunoglobulins among the intravenous and extracellular body compartments, the peak level of IgG detected immediately after transfusion is reduced by 30% within

first 24 hours of the infusion and another 40% reduction in the level is expected in one week time. The minimum Invivo half-life of gammaglobulins in IVIG 5% SXX is three weeks.

Indications & Dosage

A continuous investigation is going on to establish the role of IVIG 5% SXX in many different types of diseases. The role of IVIG in different autoimmune disorders has been a subject of special interest for many years. The disorders that have reportedly responded to IVIG 5% SXX include Idiopathic thrombocytopenic purpura[9, 11,12], Guillain –Barré syndrome[13,14], Chronic inflammatory demyelinating poly-radiculo-neuropathy[15], Myasthenia gravis[16], Multifocal motor neuropathy[17,18], Corticosteroid-resistant dermato-myositis[19], Kawasaki's disease[20], Prevention of graft-versus-host disease[21], Antineutrophil cytoplasmic-autoantibody positive vasculitis[22,23], Autoimmune uveitis[24], Multiple sclerosis[25,27] and many others.

Primary Immunodeficiencies[4,20]:

This indication is among the first approved indications of IVIG 5% SXX. The dosage used is 200-400 mg/Kg (4-8 ml/Kg) body weight. The same dose is repeated at 4 weeks intervals. Primary Immunodeficiencies include Wiskott Aldrich Syndrome, Severe Combined Immunodeficiency, X-linked hypogammaglobulinemia, hypogammaglobulinemia with hyper IgM and common variable immunodeficiency. All these immunodeficiencies are characterized as a permanent immunodeficiency state with reduced or impaired levels of immune globulins in normal serum or plasma.

Idiopathic Thrombocytopenic Purpura (ITP) [9,11]:

The classical dosage regimen used in ITP is 400 mg/Kg (8ml/Kg) body weight for consecutive 5 days. However, another suggested dosage regimen is 1000 mg/kg (20 ml/kg) body weight for one day or two consecutive days, depending upon the platelet level rise during the first 24 hours after the first dose. A maintenance dose of 400-1000 mg/Kg (8-20 ml/Kg) body weight may be given in cases where the platelet count falls below the desired levels. Current research level, cannot predict before the IVIG therapy about the extent of response of the therapy in different patients. The duration of the raised platelet level also vary in different patients.

Allogenic Bone Marrow Transplant[3,21]:

IVIG 5% SXX is given in a dosage of 500 mg/Kg (10 ml/Kg) body weight on day 7 and 2 pre-transplant and then repeated post-transplant at weekly intervals till day 90. The studies show that IVIG 5% SXX is useful in Allogenic Bone Marrow Transplants in patients with 20 years or more age. IVIG 5% SXX is found to have role in reducing the occurrence of Acute Graft vs Host Disease (AGVHD). It is also found to be effective in reducing the risk of septicemia, interstitial pneumonia, and other infections.

HIV Infection in Children[2,6,7]:

IVIG 5% SXX is given in a dosage of 400mg/Kg (8 ml/Kg) body weight after every 28 days to reduce the serious infection episodes and the hospitalization days. In children with HIV infection both cellular and Humoral immunity develop defects. As a result there are high risks of infections that may prove to be life

threatening. The opsonic and neutralizing Antibodies present in IVIG 5% SXX play an important role to reduce the risk of such infections and there is a substantial reduction in hospitalization days of the patients.

Administration:

IVIG 5% SXX should be administered at a rate of 0.01-0.02 ml/Kg body weight/minute for half an hour. If the patient tolerates it well, the rate of infusion may gradually be increased to a maximum of 0.08 ml/Kg body weight/minute. For IVIG 5% SXX the rate of administration is an important factor. In different studies conducted for determining the safe rate of reaction, it has been observed that in adults the infusion rate more than 0.06 ml/Kg/minute may shows more frequency of adverse reactions than rate less than 0.06 ml/Kg/minute. However in children, even the highest rates of infusions are well tolerated. The comfortable rates of administration for IVIG 5% SXX vary from individual to individual. So the infusion should be started at a slower rate of infusion and then gradually it should be increased, as mentioned above. For details please see the section of "Adverse Reactions". The studies about the intravenous administration of maltose solutions show that infusion rate of 0.25 g maltose/kg body weight/hour given to healthy individuals is well tolerated and the infusion rate of 0.27 to 0.62 g maltose/kg body weight/hour to normal individuals produces mild or no adverse reactions. The maximum infusion rate recommended (0.08 ml/kg body weight/minute) for IVIG 5% SXX delivers 0.48 g maltose/kg body weight/hour that is well tolerated. Excretion of maltose is through urine and is dose-dependent with mild diuresis. IVIG 5% SXX has a pH of 4.0 that is well tolerated by the blood. The buffer capacity of IVIG 5% SXX and that of blood has been studied in Phase 1 Human trials and found not to alter the arterial blood pH even in highest recommended doses. However if the patient has an impaired acid-base regulatory mechanism, then IVIG 5% SXX might be administered with caution.

Adverse Reactions:

The adverse reactions to IVIG 5% SXX are rare and are related to the infusion rate in most of the cases. In different studies, performed for different indications and in different age groups, the frequency of adverse reactions has been in a ragne of 2.6%-5.0%. 28 The symptoms include malaise, headache, nausea, vomiting, faintness, fever, chills, chest tightness and pain. Difficulty in breathing, back or hip pain and mild erythema at the site of infusion has also been reported in some cases[29, 30].

Patients with primary immunoglobulin deficiency who have never received intravenous immune globulin have a higher frequency of adverse effects than those who have been receiving regular therapy. Mild reactions to immune globulin occur within the first 30 minutes after infusion and may be relieved by reducing the infusion rate or temporarily stopping the infusion[1,29]. Acute aseptic meningitis with pleocytosis of the cerebrospinal fluid may occur within 48 to 72 hours after the administration of immune globulin. The symptoms resolve spontaneously[29] and can be prevented with nonsteroidal antiinflammatory drugs. The syndrome does not appear with further infusions of the immune globulin[1, 29].

In the studies undertaken to date, no other types of reactions have been reported with IVIG 5% SXX. Reactions to intravenous immunoglobulin tend to be related to the rate of infusion. On decreasing the

rate of infusion or stopping the infusion transiently, the reactions will subside spontaneously. After the effects are disappeared, the infusion may be restarted at a slower rate. It has also been observed that even the highest rates of infusions are well tolerated in children. In adults, infusion rates more than 0.06 ml/Kg/minute may show more frequency of adverse reactions than the infusion rates less than 0.06 ml/Kg/minute.

Very rarely, serious anaphylactoid reactions may occur within the first hour after the administration of immuneglobulin due to IgA deficiency[31,32]. The presence of anti-IgA antibodies is not, however, always associated with severe adverse reactions to immuneglobulin.True anaphylactic reactions to IVIG 5% SXX may occur in recipients with prior history of severe allergic reactions to any Human immunoglobulins (either I/M or I/V).

Contra-Indications:

IVIG 5% SXX is contraindicated in individuals known to have had an anaphylactic or severe systemic response to any Immune Globulin (Human), either intramuscular or intravenous. Individuals with selective IgA deficiencies who have known antibody against IgA (anti-IgA antibody) are also contraindicated to receive IVIG 5% SXX[31, 32].

Precautions:

Any vial that has been entered should be used promptly. Partially used vials should be discarded. Do not use if the solution is turbid or has some particulate material in it. Solution which has been frozen should not be used. The patients that are at high risk of developing renal dysfunction should be given IVIG 5% SXX at slower infusion rates (not more than 0.01 ml/Kg/minute). For such patients, renal functions should be monitored before and after the infusion.33 If some abnormality is observed, it is recommended to discontinue the administration. IVIG 5% SXX contains antibodies that may interfere with the response to live viral vaccines. Therefore, such vaccines may not be used until approximately 6 months after IVIG 5% SXX administration.

Animal reproduction studies have not been conducted with IVIG 5% SXX. So it should be used in pregnant woman only when clearly indicated.

Storage:
Store between 2-8°C.
Don’t Freeze the solution.
Don’t use after expiry date.
Should be sold against physician’s prescription only(POM).

Package:
0.5g/vial, 2.5g/vial, 5g/vial

Ratification:
Chinese drug permission S20033041 0.5g/vial
Chinese drug permission S20013041 2.5g/vial

Chinese drug permission S20033043 5g/vial

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