

# Omr- IgG –am™ 5% IV

## Nanofiltered and SD virus inactivated

**Composition:**

**Omr- IgG –am™ 5% IV** is a sterile solution containing 5% protein (50 mg in 1 ml solution of which at least 95% is Human Normal Immunoglobulin G as the active ingredient), 10% maltose, and Water for Injections. The Immunoglobulin A (IgA) content is  $\leq 0.15\text{mg/ml}$ .

**Omr- IgG –am™ 5% IV does not contain Sucrose.**

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**Description**

**Omr- IgG –am™ 5% IV** is manufactured from human plasma by Cohn (ethanol) fractionation (this step has been shown in literature to be a primary virus inactivation step). After a first ultra - /diafiltration, the product undergoes a second virus inactivation step by the solvent-detergent method using TnBP/Triton-X-100, and a third inactivation by nanofiltration at pH-4.

**Pharmaceutical Form**

**Omr- IgG –am™ 5% IV** is a clear or slightly opalescent, almost odorless, colorless to pale yellow liquid for intravenous infusion.

**Pharmacological Properties****Pharmacodynamic properties**

As Human Normal Immunoglobulin, the product contains mainly IgG having a broad spectrum of antibodies against various infectious agents (viruses and bacteria) currently prevalent in the population. Opsonization and neutralization of micro-organisms and toxins have been documented.

**Omr- IgG –am™ 5% IV** contains all the immunoglobulin G activities which are present in the normal population. It is prepared from pooled source material from not fewer than 1000 prescreened donors.

The product has a distribution of IgG sub-classes closely proportional to that of normal human plasma.

Sub-classes IgG	Human Plasma	Omr- IgG –am™ 5% IV
IgG1	60.0 %	63.6% $\pm$ 3.8
IgG2	29.4 %	29.4% $\pm$ 4.7
IgG3	6.5 %	5.8% $\pm$ 0.8
IgG4	4.1 %	1.2% $\pm$ 0.3

Adequate doses of this medicinal product may restore abnormally low IgG levels to the normal range. The mechanism of action in idiopathic thrombocytopenic purpura is not fully elucidated.

**Pharmacokinetic properties**

Human Normal Immunoglobulin IV is immediately and completely bioavailable in the recipient's circulation after intravenous administration. It is distributed relatively rapidly between plasma and extravascular fluid; after approximately 3-5 days an equilibrium is reached between the intra- and extravascular compartments.

Human Normal Immunoglobulin IV has a half-life of between 26 and 32 days. This half-life may vary from patient to patient, in particular in primary immunodeficiency.

Immunoglobulin G (IgG) and IgG-complexes are broken down in cells of the reticuloendothelial system.

**Preclinical safety data**

Immunoglobulins are normal constituents of the human body.

In animals, single dose toxicity testing is of no relevance and higher doses result in overloading. Repeated dose toxicity testing and embryo-foetal toxicity studies are impracticable due to induction of, and interference with antibodies. Effects of the product on the immune system of the new-born have not been studied.

Since clinical experience provides no indication of tumorigenic or mutagenic effects of immunoglobulins, experimental studies, particularly in heterologous species, are not considered necessary.

Virus inactivation of **Omr- IgG –am™ 5% IV** has been carried out using solvent/detergent method with tri-n-butyl phosphate (TnBP) and Triton-X-100. These SD reagents are removed during the purification process.

At the doses at which **Omr- IgG –am™ 5% IV** is administered, no toxic effects have occurred with these reagents in animal studies of single dose and repeated dose toxicity, and of reproduction toxicity.

**Therapeutic Indications**

- Primary immunodeficiency (patients with primary defective antibody synthesis such as agammaglobulinemia or hypogammaglobulinemia)
- Idiopathic Thrombocytopenic Purpura (ITP)
- Chronic Lymphatic Leukemia (CLL) with severe secondary hypogammaglobulinemia and recurrent infections.

**Contraindications**

**Omr- IgG –am™ 5% IV** is contra- indicated in individuals who are known to have anaphylactic or severe systemic response to intramuscular or intravenous immunoglobulin preparations.

As with other immunoglobulin preparations **Omr- IgG –am™ 5% IV** should not be given to patients with antibodies to IgA or selective IgA deficiency.

**Warnings and Special Precautions**

Certain severe adverse drug reactions may be related to the rate of infusion. Patients naive to immunoglobulin G (IgG) usually experience a higher frequency of minor events than those well maintained on regular therapy. The recommended infusion rate given under "Dosage and Administration" must be closely followed and patients must be closely monitored and carefully observed for any symptoms throughout the infusion period, and for 1 hour after the first infusion. In case of adverse reactions either the rate of administration must be reduced or the infusion stopped until symptoms disappear.

If severity of reactions persists after discontinuation of the infusion, appropriate treatment is recommended.

In case of anaphylactic reaction or shock, treatment should follow the guidelines for shock therapy. Epinephrine should be available for the treatment of any acute anaphylactoid reactions. Patients with agammaglobulinemia or extreme hypogammaglobulinemia who have not received immunoglobulin therapy within the preceding 8 weeks may be at risk of developing inflammatory reactions upon the infusion of human immunoglobulins. These reactions are manifested by a rise in temperature, chills, nausea and vomiting, and appear to be related to the rate of infusion.

In patients at risk of renal failure with diabetes or those with systemic lupus erythematosus and renal involvement, creatinine, levels should be measured for 3 days after intravenous immunoglobulin infusion.

Patients should be observed for at least 20 minutes after administration.

Any vial that has been entered should be used promptly. Partially used vials should be discarded. Do not use if turbid. Solutions which have been frozen should not be used.

An aseptic meningitis syndrome (AMS) has been reported to occur infrequently in association with Immune Globulin Intravenous (Human) treatment. The syndrome usually begins within several hours to two days following Immune Globulin Intravenous (Human) treatment. It is characterized by symptoms and signs including severe headache, nuchal rigidity, drowsiness, fever, photophobia, painful eye movements, and nausea and vomiting. Cerebrospinal fluid studies are frequently positive with pleocytosis up to several thousand cells per mm<sup>3</sup>, predominantly from the granulocytic series, and elevated protein levels up to several hundred mg/dL. Patients exhibiting such symptoms and signs should receive a thorough neurological examination, including CSF studies, to rule out other causes of meningitis. AMS may occur more frequently in association with high dose (2g/kg) Immune Globulin Intravenous (Human) treatment.

Discontinuation of Immune Globulin Intravenous (Human) treatment has resulted in remission of AMS within several days without sequelae.

**Drug interactions and other forms of interactions**

- Live attenuated vaccines  
Immunoglobulin administration may impair for a period of at least 3 months the efficacy of live attenuated virus vaccines such as measles, rubella, mumps, and varicella.
- Interference with serological testing  
Passive transmission of antibodies to erythrocyte antigen- e.g. A, B or D may interfere with some serological tests- e.g. Coombs test, haptoglobin, reticulocyte count.
- Incompatibilities

**Omr- IgG —am™ 5 % IV** should not be mixed with other medicinal products. A separate intravenous line should be used for the infusion.

**Pregnancy and lactation**

IGIV crosses the placenta. IGIV should be administered to pregnant women only if clearly needed. Past experience with immune globulin intramuscular has shown no adverse effect on the fetus; however, it is not known whether IGIV can cause harm to the fetus. Although studies specific for pregnancy have not been done in humans, other studies on the use of IGIV during pregnancy for treatment of disease have not shown IGIV to cause harm to the fetus. Studies have not been done in animals. FDA Pregnancy Category C.

**Breast-feeding**

It is not known whether IGIV is distributed into breast milk. However, problems in humans have not been documented

**Effects on ability to drive and use machines**

There is no indication that immunoglobulins may impair the ability to drive and use machines.

**Adverse reactions**

During or shortly after the application of intravenous immunoglobulins minor side effects such as headache, chills, fever, vomiting, allergic reactions, nausea, athralgia, and mild back pain may occur occasionally. Dyspnea and tachycardia may occur more frequently and require medical attention. Reversible aseptic meningitis and nephrotoxicity have occurred rarely. Rarely immunoglobulins may cause a fall in blood pressure and, in isolated cases, anaphylactic shock, even when the patient has shown no sensitivity to previous administration. Slowing or stopping the infusion should allow the symptoms to disappear promptly. Thereafter the infusion may be started again using a lower infusion rate. Allergic and anaphylactic reactions necessitate immediate cessation of the infusion. Less severe reactions may be controlled with glucocorticoids and/or antihistamines. When severe reactions occur, treatment for shock must be initiated according to current guidelines. For this purpose, see the recommendations given in the following table.

**Immediate measures to be taken in case of intolerable reactions:**

Clinical symptoms	Measures
Subjective complaints (backache, nausea, etc.)	Stop infusion
Skin symptoms (flush, urticaria, etc.)	Antihistamines
Tachycardia, moderate drop in blood pressure (below 90 mm Hg systolic)	Glucocorticoids i.v. (100-500 mg prednisolone)
Dyspnea Shock	Dopamine continuous infusion (2-4 µg/kg/min) high doses of glucocorticoids i.v. (up to 1 g prednisolone [water soluble]), oxygen, volume expander, possibly increased diuresis using furosemide in case of normovolaemia, control of acid base balance and electrolytes (if necessary, correct).
Persistent normovolaemic shock	Dopamine dosage up to a maximum of 10 µg/kg/min possibly in combination with noradrenalin.
Cardiac or respiratory arrest	Resuscitation

When medicinal products prepared from human blood or plasma are administered infectious diseases due to transmission of infective agents cannot be totally excluded. This also applies to pathogens of hitherto unknown nature.

To reduce the risk of transmission of infective agents, selection of donors and donations by suitable measures is performed, plasma pools are tested, and removal and/or inactivation procedures are included in the production process.

For **Omr- IgG —am™ 5% IV**, the manufacturing process contains 3 virus inactivation steps: Cohn fractionation (ethanol), solvent/detergent treatment (TnBP +Triton-X-100) and nanofiltration at pH-4. Reduction of infective agents during the OMR- IgG -AM 5% manufacturing process:

Nine viruses have been included in viral safety studies,

- Type 1 human immunodeficiency virus HIV-1 (RNA-enveloped)(AIDS)
- Sindbis virus (RNA-enveloped)(model for HCV)
- Type 1 Poliovirus (RNA-naked)(model for HAV)
- Pseudorabies virus (PRV)(DNA-enveloped)(model for Herpes)
- Bovine viral diarrhea virus (BVDV) (RNA-enveloped)(model for HCV)
- Polyomavirus maccacae SV40 (DNA-naked)
- Vesicular stomatitis virus (VSV)(RNA-enveloped)
- Hepatitis A virus (RNA-Naked)
- Minute Virus of Mice (MVM) (DNA-Naked) (model for Parvo virus B-19)

Virus	HIV-1	Sindbis	PRV	Poliovirus	VSV	SV40	BVDV	HAV	MVM
Cohn*	≥5.50	≥6.36	≥7.28	≥3.80	not done	≥5.51	not done	not done	not done
S/D step	>4.01	≥5.20 *	>4.01	not done	≥5.30 *	not done	>4.94	1.76	not done
Nanofiltration	>5.18	not done	>5.03	not done	not done	not done	4.34	>7.31	1.51

\* results based on literature.

**Dosage**

The dose and dosage regimen is dependent on the indication (replacement or immunomodulation) and on the in-vivo half life in individual patients.

Because of this dosage regimen may need to be individualized for each patient, the following dosage regimens are given as a guideline.

**• Replacement therapy in Primary Immunodeficiencies and Immunodeficiency secondary to Chronic Lymphatic Leukemia (CLL).**

The dosage regimen should achieve a trough level of immunoglobulin G (IgG) (measured before the next infusion) of at least 4-6 g/L. Three to six months are required after the initiation of therapy for equilibration to occur. The recommended starting dose is 0.4-0.8 g/kg depending of the circumstances (e.g. active infection) followed by 0.2 g/kg every three weeks.

The dose required to achieve a trough level of 6 g/L are of the order of 0.2-0.8 g/kg/month.

The dosage interval when steady state has been reached varies from 2-4 weekly.

Trough levels should be measured in order to adjust the dose and the dosage interval.

**• Idiopathic Thrombocytopenic Purpura**

For the treatment of an acute episode, 0.8-1 g/kg on day one, repeated on day three if necessary, or 0.4 g/kg daily for two to five days. The treatment can be repeated if relapse occurs. In the first treatment regimen, if an adequate increase in the platelet count is observed at 24 hours, the second dose of 1000 mg/kg body weight may be withheld. The high dose regimen (1,000 mg/kg x 1-2 days) is not recommended for individuals with expanded fluid volumes or where fluid volume may be a concern.

**Administration**

**Omr- IgG —am™ 5 % IV** should be infused intravenously at an initial rate of 0.01-0.02 ml/kg/min for 15 minutes, increasing gradually to a maximum of 0.08 ml/kg/min. However it is recommended not to exceed a rate of 3 ml/min.

**Overdose**

Consequences of overdosage are not known.

**How Supplied**

**Omr- IgG —am™ 5% IV** is available in the following package sizes:

Volume	Protein-content
50 ml	2.5 g
100 ml	5.0 g
200 ml	10.0 g

**Storage Conditions**

Vials should be stored at a temperature lower than 25°C, protected from light. Do not freeze!

**Registration No.: 1038028952**

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