

## Normal Immunoglobulin for Intravenous use B.P.

*ImmunoRel*<sup>®</sup> 5 % solution**DESCRIPTION**

*ImmunoRel*<sup>®</sup> is a solvent/detergent treated, sterile, preparation of chromatographically purified immunoglobulin G (IgG) derived from pooled human plasma. The product is manufactured by modified Cohn's fractionation process followed by ultra-filtration and ion exchange chromatography. The manufacturing process includes treatment with an organic solvent detergent mixture composed of Tri-n-butyl phosphate and TritonX-100. The manufacturing process provides a significant viral reduction as confirmed by in-vitro studies.

The manufacturing process isolates IgG without additional chemical or enzymatic modification and the Fc portion is maintained intact. This contains all the IgG antibody activities against bacterial and viral agents that are capable of opsonisation and neutralisation of microbes and toxins, which are present in the normal donor population. The IgG subclass distribution is also very similar to that in normal plasma. This product contains only trace amounts of IgA ( $\leq 6$  mg/l). Maltose is used as a stabiliser in the concentration of 100g/l.

**COMPOSITION**

*ImmunoRel*<sup>®</sup> is available in 5% concentration solution in 50ml preparations.

Each vial contains:

Immunoglobulin G	50 g/l
Stabiliser Maltose	100 g/l
IgA content	6 mg/l
Immunoglobulin sub class	Normal distribution

**CLINICAL PHARMACOLOGY****Pharmacodynamics**

Immunoglobulin is an immuno-modulating agent that has multiple actions:

1. Saturation of Fc receptors on macrophages
2. Modulation of complement activation
3. Suppression of idiotypic antibodies
4. Suppression of various inflammatory mediators, including cytokines, chemokines, and metalloproteinases.

The Fc region of IgG facilitates interaction with and signaling through Fc receptors on phagocytes, B cells, and other cells and with Fc-binding plasma proteins (e.g., components of the complement system). Blockade of macrophage Fc receptors is considered the primary mechanism of action of immune globulin in persons with Idiopathic thrombocytopenic purpura (ITP) and other autoantibody mediated cytopenias. In persons with Kawasaki disease, IVIG is thought to inhibit the generation of membrane attack complexes (C5b-C9) and subsequent complement-mediated tissue damage by binding the activated components C3b and C4b, thus preventing their deposition on target surfaces. In persons with dermatomyositis, IVIG induces a decrease in plasma levels of membrane attack complex and a substantial decrease in the amounts of C3b and membrane attack complex deposited in endomysial capillaries. The high content of anti-idiotypes against autoantibodies in IVIG facilitates its ability to neutralize autoantibodies, as is shown in patients with acquired haemophilia due to autoantibodies against factor VIII. Specific effects of Immunoglobulin have been described. The results of in-vitro C3 uptake studies and the effect of IVIG on the clearance of pre-opsonized cells suggest that IVIG produces a kinetic depression of C3 uptake and modifies the process of complement fragment deposition on erythrocytes.

Immunoglobulin contains natural antibodies, accounting for some of its effects. Normal serum contains IgG, IgM, and IgA antibodies, which are referred to as natural antibodies because they are induced without deliberate immunization and are independent of antigenic exposure. They are considered key to the immuno-regulatory effects of immune globulin in immune-mediated disorders.

**Pharmacokinetics****In normal subjects**

Intravenous immunoglobulin, (*ImmunoRel*<sup>®</sup>) contains all the IgG antibody activities against bacterial and viral agents that are capable of opsonisation and neutralisation of microbes and toxins, which are present in the normal donor population.

Peak serum concentrations occur immediately after intravenous injection of immunoglobulin preparation and are dose-related. Within 24 hours, up to 30% of a dose may be removed by catabolism and distribution. Data concerning distribution suggests that IVIG distribute throughout intravascular (60%) and extra-vascular (40%) spaces, crosses the placenta (in increasing amounts after 30 weeks of gestation), and may be excreted into milk. The serum half-life of immunoglobulin ranges between 21 to 29 days. This will however vary from person to person and can be affected by hyper metabolic states.

**In primary immunodeficiencies**

This product is not advocated in patients with isolated IgA deficiencies. As per data stated in various clinical studies, the half-life of IgG (in patients suffering from primary immunodeficiency conditions) varies between 26 to 35 days as compared to 21 to 29 days in normal subjects.

**In secondary immunodeficiencies**

Compared with the average half-life of 22 days in normal subjects, the half-life in bone marrow transplant patients can be shorter, and will depend on the level of bacterial infections or superimposed viral and fungal infections.

**In neonates**

Single dose pharmacokinetic study of intravenous immunoglobulin with 500, 750 and 1000 mg/kg in neonates with birth weights ranging from 750 to 1500 gms generally shows a mean elimination half-life being shorter as compared to normal subjects.

**PRODUCT SAFETY**

The manufacturing process for *ImmunoRel*<sup>®</sup> uses plasma collected from approved blood banks where the donors are screened for their history as per guidelines laid down by the regulatory authorities. Their blood is screened for the mandatory infectious diseases. These are repeat donors whose samples are quarantined and re-tested. Only on being declared negative the plasma is used for processing.

After manufacturing, the product is tested by suitable methods to show negative from viruses like HIV, HBV, HCV, Parvovirus and HAV. The manufacturing procedure incorporates the well-known time tested and proven method of Solvent Detergent Technology, which inactivates lipid-coated viruses. Multiple steps have been employed to assure product safety hence there is a very remote probability that unknown infectious agents may be present in these products like lesser known viruses and theoretical CJD (Creutzfeldt Jakob disease).

Validation studies were carried out to validate the efficiency of the manufacturing process to remove and/or inactivate viruses. The manufacturing processes with the incorporated viral inactivation procedures have been validated as per recommendations and guidelines provided by the committee for proprietary medicinal products (CPMP guidelines).

These studies were conducted using starting intermediate samples spiked with model viruses to represent the worst-case conditions. Appropriate samples were drawn for viral titer determinations from manufacturing intermediates keeping in mind the process parameters, characterizations and final product quality meet the regulatory requirement.

**INDICATIONS**

Immunoglobulin preparations are indicated in several clinical conditions. An approved list of clinical conditions where *ImmunoRel*<sup>®</sup> is indicated, is as under:

# Primary Immunodeficiency (PID)	# Kawasaki Syndrome	# Idiopathic Thrombocytopenic Purpura
# B-cell Chronic lymphocytic leukemia	# Paediatric HIV 1 infection	# Hemopoietic stem cell transplantation in elderly

**DOSAGE**

Treatment dosage varies according to the indication and preparation used. IVIG for a patient should be adjusted according to clinical response. The following are dosage schedule guidelines:

**Note:** Doses and frequency must be based primarily on clinical course and response.

Indication	Dose
Replacement therapy in Primary Immunodeficiency (PID)	Starting dose: 0.4-0.8 g/kg followed by 0.2-0.8 g/kg every 2-4 weeks to obtain IgG trough level of at least 4-6 g/l
Replacement therapy in Secondary immunodeficiency (SID)	0.2-0.4 g/kg every 3-4 weeks to obtain IgG trough level of at least 4-6 g/l
<b>Allogeneic Bone marrow Transplantation (BMT):</b>	
(1) Treatment of infections and prophylaxis of graft versus host disease	0.5 g/kg every week from day 7 up to 3 months after transplantation.
(2) Persistent lack of antibody production	0.5 g/kg every month until antibody levels return to normal
Idiopathic Thrombocytopenic Purpura (ITP)	0.8 - 1 g/kg on day 1, possibly repeated once within 3 days or 0.4 g/kg/d for 2 - 5 days
Kawasaki disease	1.6 - 2 g/kg in several doses for 2 - 5 days in association with acetylsalicylic acid or 2 g/kg in one dose in association with acetylsalicylic acid
Paediatric HIV	0.2 - 0.4 g/kg every 3 - 4 weeks
Guillain Barré syndrome (GBS)	0.4 g /kg/d for 3 -7 days

Source - EMEA

IVIG should be used with caution in patients with pre-existing renal insufficiency and in patients judged to be at increased risk of developing renal insufficiency (including, but not limited to those with diabetes mellitus, age greater than 65 years, volume depletion, para-proteinemia, sepsis, and patients receiving known nephro-toxic drugs).

In these cases especially it is important to assure that patients are not volume depleted prior to immunoglobulin infusion.

The first infusion of immunoglobulin preparation should start at the initial rate of 0.6 to 1.2 ml/ kg of body weight /hour for the first thirty minutes and can be increased up to 2.4 ml/ kg of body weight /hour. Subsequent infusion to the same patient may be increased to 4.8 ml/ kg of body weight /hour.

The first infusion of immunoglobulin in previously untreated agammaglobulinemic and hypogammaglobulinemic patients may lead to systemic side effects. The nature of these effects has not been fully elucidated. Some of them may be due to the release of pro-inflammatory cytokines by activated macrophages in immunodeficient recipients. Subsequent administration of immunoglobulin to immunodeficient patients as well as to normal individuals usually does not cause further untoward side effects.

**CONTRAINDICATIONS**

Intravenous immunoglobulin is contraindicated in patients with selective IgA deficiency, who possess antibody to IgA. Immunoglobulin preparation may also be contraindicated in patients who have a previous history of severe systemic reactions to the intravenous or intramuscular administration of human immunoglobulin.

**ADVERSE REACTIONS**

Adverse reactions such as pain, headache and chills may be seen in patients with immunodeficiency.

Inflammatory adverse reactions have been described in agammaglobulinemic and hypogammaglobulinemic patients who have never received immunoglobulin substitution therapy before or in patients whose time from last treatment is greater than 8 weeks and whose initial infusion rate exceeds 20 drops (1 ml) per minute. This occurs in approximately 10% of such cases. Such reactions may also be observed in some patients during chronic substitution therapy.

These reactions, which generally become apparent only 30 minutes to 1 hour after the beginning of the infusion, are flushing of the face, feelings of tightness in the chest, chills, fever, dizziness, nausea, diaphoresis, and hypotension. In such cases the infusion should be temporarily stopped until the symptoms have subsided.

*ImmunoRel*<sup>®</sup> although contains only trace amounts of IgA  $\leq 6$ mg/l, it is not indicated in patients with IgA deficiencies. In such cases there is a fair amount of risk of anaphylactic reactions to the product.

Increases in creatinine and blood urea nitrogen (BUN) have been observed as soon as one to two days following infusion. Progression to oliguria or anuria may require dialysis. Severe occasional renal adverse events that have been reported following IVIG therapy include: acute renal failure, acute tubular necrosis, proximal tubular nephropathy and osmotic nephrosis.

Very rarely, mild haemolysis have been reported after infusion of intravenous immunoglobulin products. These were attributed to transferrals of blood group e.g., anti-D antibodies.

**Alternative routes of administration**

Several intravenous immunoglobulin preparations have been given to patients by alternative routes like intraperitoneal, intrathecal, intraventricular, oral etc. very successfully. Physicians desirous of knowing more on these alternative routes of administration are recommended to refer to relevant literature.

IVIG, in general, has been known to be administered for prophylaxis and treatment of peritoneal infections after major abdominal surgery through intraperitoneal route and through intraventricular route for meningococcal meningitis and enterovirus encephalitis.

IVIG has also been administered in patients with primary immunodeficiency syndromes to reduce the risk of repeated infection introduced by repeated connections to permanent indwelling catheters through subcutaneous route.

**WARNING AND PRECAUTIONS**

Prior to initiation of immunoglobulin therapy, it is essential to correct volume depletion of the patient by infusing appropriate fluids. Periodic monitoring of renal function tests and urine output is particularly important in patients judged to have a potential increased risk for developing acute renal failure. Renal function, including measurement of blood urea nitrogen (BUN), serum creatinine, should be assessed prior to the initial infusion of immunoglobulin and again at appropriate intervals thereafter. If renal function deteriorates, discontinuation of the product should be considered.

It is generally advisable not to dilute plasma derivatives with other infusible drugs. *ImmunoRel*<sup>®</sup> should be given by a separate infusion line. No other medications or fluids should be mixed with the *ImmunoRel*<sup>®</sup> preparation.

**Pregnancy and Lactation**

Pregnancy Category C: Animal reproduction studies have not been conducted with *ImmunoRel*<sup>®</sup>. It is also not known whether *ImmunoRel*<sup>®</sup> can cause foetal harm when administered to a pregnant woman or can affect reproduction capacity. This preparation should be given to a pregnant woman only if clearly needed.

Intact immune globulins such as those contained in *ImmunoRel*<sup>®</sup> cross the placenta from maternal circulation increasingly after 30 weeks gestation. In cases of maternal ITP where IVIG was administered to the mother prior to delivery, the platelet response and clinical effect were similar in the mother and neonate.

**Pediatric & Geriatric population**

High dose administration of IVIG in pediatric patients with acute or chronic Immune Thrombocytopenic Purpura has not revealed any pediatric-specific hazard.

Antibodies in IVIG, may impair the efficacy of live attenuated viral vaccines such as measles, rubella, and mumps. Immunizing physicians should be informed of recent therapy with IVIG so that appropriate precautions may be taken.

**STORAGE**

Store between 2°C and 8°C. Do not freeze.

Discard any unused material or half empty vials.

**SHELF LIFE**

36 months.

**PRESENTATION**

Immunoglobulin Intravenous (Human), *ImmunoRel*<sup>®</sup> is available as 50ml intravenous infusion.

**References:**

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