Summary of Product Characterization

ImmunoRel® 5 % solution, Normal Immunoglobulin for Intravenous Administration

1. NAME OF THE MEDICINAL PRODUCT

Immunoglobulin Intravenous (Human), ImmunoRel® is available as 10ml, 20ml, 50ml and 100 ml intravenous infusion.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

ImmunoRel® is available in 5% concentration solution in 10ml, 20ml, 50ml and 100ml preparations.

Each bottle contains :	10 ml	20 ml	50 ml	100 ml
Protein Content	50 g/l	50 g/l	50 g/l	50 g/l
IgG	0.5 g	1g	2.5 g	5 g
Stabiliser Maltose	100 g/l	100 g/l	100 g/l	100 g/l
IgA content	≤ 80 mg/l	≤ 80 mg/l	≤ 80 mg/l	≤ 80 mg/l
IgG subclass	Normal distribution	Normal distribution	Normal distribution	Normal distribution

3. PHARMACEUTICAL FORM

Solution for infusion. A clear or slightly opalescent and colourless or pale yellow liquid.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

Immunoglobulin preparations are indicated in several clinical conditions. An approved list of clinical conditions where ImmunoRel® 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

4.2 Posology and Method of Administration

Treatment dosage varies according to the indication and preparation used. IVIg for a patient should be adjusted according to clinical response.

4.2.1 Posology

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
Allogeneic Bone marrow Transplantation (BMT): (1) Treatment of infections and prophylaxis of graft versus host disease (2) Persistent lack of antibody production	0.5 g/kg every week from day 7 up to 3 months after transplantation. 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

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.

4.2.2 Method of Administration

The first infusion of immunoglobulin preparation should start at the initial rate of 0.6 to1.2 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.

Patients should be observed for at least 20 minutes after administration. In case of shock, treatment should follow the guidelines for shock therapy.

4.3 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.

4.4 Special Warnings and Special Precautions for Use

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.

In case of adverse reaction, either the rate of administration must be reduced or the infusion stopped. The treatment required depends on the nature and severity of the side effect.

In case of shock, standard medical treatment for shock should be implemented.

Standard measures to prevent infections resulting from the use of medicinal products prepared from human blood or plasma include selection of donors, screening of individual donations and plasma pools for specific markers of infection and the inclusion of effective manufacturing steps for the inactivation/removal of viruses.

Despite this, when medicinal products prepared from human blood or plasma are administered, the possibility of transmitting infective agents cannot be totally excluded. This also applies to unknown or emerging viruses and other pathogens.

The measures taken are considered effective for enveloped viruses such as HIV, HBV and HCV. The measures taken may be of limited value against non-enveloped viruses such as HAV and parvovirus

B19.There is a reassuring clinical experience regarding the lack of hepatitis A or parvovirus B19 transmission with immunoglobulins and it is also assumed that the antibody content makes an important contribution to the viral safety.

It is strongly recommended that every time that ImmunoRel® 5 % solution is administered to a patient, the name and batch number of the product are recorded in order to maintain a link between the patient and the batch of the product.

When administered in high dose over a relatively short period of time, signs and symptomatology of fluid overload may result, especially in susceptible patients such as small children, elderly individuals or patients with renal impairment.

Certain severe adverse drug reactions may be related to the rate of infusion.

Patients must be closely monitored and carefully observed for any symptoms throughout the infusion period. Certain adverse reactions may occur more frequently.

• in case of high rate of infusion;

• in patients with hypo- or agammaglobulinemia with or without IgA deficiency;

• in patients who receive human normal immunoglobulin for the first time, or in rare cases, when the human normal immunoglobulin product is switched or when there has been a long interval since the previous infusion.

Rarely, human normal immunoglobulin can induce a fall in blood pressure with anaphylactic reaction, even in patients who had tolerated previous treatment with human normal immunoglobulin.

Patients with antibodies to IgA or with IgA deficiencies that are a component of an underlying primary immunodeficiency disease for which IVIG therapy is indicated may be at increased risk of anaphylactic reaction.

Patients who have had a severe hypersensitivity reaction to other intravenous gammaglobulin preparations should only receive Immunorel with utmost caution and in a setting where supportive care is available for treating life-threatening reactions

Potential complications can often be avoided by ensuring:

-that patients are not sensitive to human normal immunoglobulin by initially injecting the product slowly (0.5 mL/kg/min);

- that patients are carefully monitored for any symptoms throughout the infusion period.

In particular, patients naïve to human normal immunoglobulin, patients switched from an alternative IVIg product or when there has been a long interval since the previous infusion should be monitored during the first infusion and for the first hour after the first infusion, in order to detect potential adverse signs. All other patients should be observed for at least 20 minutes after administration;

- that the glucose content (max. content of 0.4g/g of IgG) is taken into account in case of latent diabetes (where transient glycosuria could appear), diabetes, or in patients on a low sugar diet.

Cases of acute renal failure have been reported in patients receiving IVIg therapy. In most cases, risk factors have been identified, such as pre-existing renal insufficiency, diabetes mellitus, hypovolemia, overweight, concomitant nephrotoxic medicinal products or age over 65.

In cases of renal impairment, IVIg discontinuation should be considered. While these reports of renal dysfunction and acute renal failure have been associated with the use of many of the licensed IVIg products, those containing sucrose as a stabilizer accounted for a disproportionate share of the total number. In patients at risk, the use of IVIg products that do not contain sucrose may be considered.

In patients at risk for acute renal failure or thromboembolic adverse reactions, IVIg products should be administered at the minimum rate of infusion and dose practicable.

In all patients IVIg administration requires:

- adequate hydration prior to initiation of the infusion of IVIg

- monitoring of urine output

- monitoring of serum creatinine levels

- avoidance of concomitant use of loop diuretics.

In case of adverse reaction, either the rate of administration must be reduced or the infusion stopped. The treatment required depends on the nature and severity of the side effect. In case of shock, standard medical treatment for shock should be implemented.

After administration of this product, an interval of 3 months should elapse before vaccination with live attenuated virus vaccines. In the case of measles, this impairment may persist for up to 1 year. Therefore patients receiving measles vaccine should have their antibody status checked.

Infusion reaction

Certain adverse reactions (e.g. headache, flushing, chills, myalgia, wheezing, tachycardia, lower back pain, nausea, and hypotension) may be related to the rate of infusion. The recommended infusion rate given under section 4.2 must be closely followed. Patients must be closely monitored and carefully observed for any symptoms throughout the infusion period.

Adverse reactions may occur more frequently

• in patients who receive human normal immunoglobulin for the first time or, in rare cases, when the human normal immunoglobulin product is switched or when there has been a long interval since the previous infusion

• in patients with an untreated infection or underlying chronic inflammation

Hypersensitivity

Hypersensitivity reactions are rare.

Anaphylaxis can develop in patients

• with undetectable IgA who have anti-IgA antibodies

• who had tolerated previous treatment with human normal immunoglobulin

In case of shock, standard medical treatment for shock should be implemented.

Thromboembolism

There is clinical evidence of an association between IVIg administration and thromboembolic events such as myocardial infarction, cerebral vascular accident (including stroke), pulmonary embolism and deep vein thromboses which is assumed to be related to a relative increase in blood viscosity through the high influx of immunoglobulin in at-risk patients. Caution should be exercised in prescribing and infusing IVIg in obese patients and in patients with pre-existing risk factors for thrombotic events (such as advanced age, hypertension, diabetes mellitus and a history of vascular disease or thrombotic episodes, patients with acquired or inherited thrombophilic disorders, patients with prolonged periods of immobilisation, severely hypovolaemic patients, patients with diseases which increase blood viscosity).

In patients at risk for thromboembolic adverse reactions, IVIg products should be administered at the minimum rate of infusion and dose practicable.

Acute renal failure

Cases of acute renal failure have been reported in patients receiving IVIg therapy. In most cases, risk factors have been identified, such as pre-existing renal insufficiency, diabetes mellitus, hypovolaemia, overweight, concomitant nephrotoxic medicinal products or age over 65.

Renal parameters should be assessed prior to infusion of IVIg, particularly in patients judged to have a potential increased risk for developing acute renal failure, and again at appropriate intervals. In patients at risk for acute renal failure, IVIg products should be administered at the minimum rate of infusion and dose practicable.

In case of renal impairment, IVIg discontinuation should be considered.

While reports of renal dysfunction and acute renal failure have been associated with the use of many of the licensed IVIg products containing various excipients such as sucrose, glucose and maltose, those containing sucrose as a stabiliser accounted for a disproportionate share of the total number.

Aseptic meningitis syndrome (AMS)

Aseptic meningitis syndrome has been reported to occur in association with IVIg treatment.

The syndrome usually begins within several hours to 2 days following IVIg treatment. Cerebrospinal fluid studies are frequently positive with pleocytosis up to several thousand cells per mm^3, predominantly from the granulocytic series, and elevated protein levels up to several hundred mg/dl.

AMS may occur more frequently in association with high-dose (2 g/kg) IVIg treatment.

Patients exhibiting such signs and symptoms should receive a thorough neurological examination, including CSF studies, to rule out other causes of meningitis.

Discontinuation of IVIg treatment has resulted in remission of AMS within several days without sequelae.

Haemolytic anaemia

IVIg products can contain blood group antibodies which may act as haemolysins and induce in vivo coating of red blood cells with immunoglobulin, causing a positive direct antiglobulin reaction (Coombs' test) and, rarely, haemolysis. Haemolytic anaemia can develop subsequent to IVIg therapy due to enhanced red blood cells (RBC) sequestration. IVIg recipients should be monitored for clinical signs and symptoms of haemolysis. (See section 4.8.)

Neutropenia/Leukopenia

A transient decrease in neutrophil count and/or episodes of neutropenia, sometimes severe, have been reported after treatment with IVIgs. This typically occurs within hours or days after IVIg administration and resolves spontaneously within 7 to 14 days.

Transfusion related acute lung injury (TRALI)

In patients receiving IVIg, there have been some reports of acute non-cardiogenic pulmonary oedema [Transfusion Related Acute Lung Injury (TRALI)]. TRALI is characterised by severe hypoxia, dyspnoea, tachypnoea, cyanosis, fever and hypotension. Symptoms of TRALI typically develop during or within 6 hours of a transfusion, often within 1-2 hours. Therefore, IVIg recipients must be monitored for and

IVIg infusion must be immediately stopped in case of pulmonary adverse reactions. TRALI is a potentially life-threatening condition requiring immediate intensive-care-unit management.

Interference with serological testing

After the administration of immunoglobulin the transitory rise of the various passively transferred antibodies in the patient's blood may result in misleading positive results in serological testing.

Passive transmission of antibodies to erythrocyte antigens, e.g. A, B, D may interfere with some serological tests for red cell antibodies for example the direct antiglobulin test (DAT, direct Coombs' test).

Transmissible agents

Standard measures to prevent infections resulting from the use of medicinal products prepared from human blood or plasma include selection of donors, screening of individual donations and plasma pools for specific markers of infection and the inclusion of effective manufacturing steps for the inactivation/removal of viruses. Despite this, when medicinal products prepared from human blood or plasma are administered, the possibility of transmitting infective agents cannot be totally excluded. This also applies to unknown or emerging viruses and other pathogens.

The measures taken are considered effective for enveloped viruses such as human immunodeficiency virus (HIV), hepatitis B virus (HBV) and hepatitis C virus (HCV). The measures taken may be of limited value against non-enveloped viruses such as hepatitis A virus and parvovirus B19.

There is reassuring clinical experience regarding the lack of hepatitis A or parvovirus B19 transmission with immunoglobulins and it is also assumed that the antibody content makes an important contribution to the viral safety.

It is strongly recommended that every time that IVIg is administered to a patient, the name and batch number of the product are recorded in order to maintain a link between the patient and the batch of the product.

Paediatric population

The special warnings and precautions for use mentioned for the adults should also be considered for the paediatric population.

4.5 Interactions with other Medicinal Products and other Forms of Interaction

It is generally advisable not to dilute plasma derivatives with other infusible drugs. ImmunoRel® should be given by a separate infusion line.

No other medications or fluids should be mixed with the ImmunoRel® preparation.

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.

After administration of this product, an interval of 3 months should elapse before vaccination with live attenuated virus vaccines. In the case of measles, this impairment may persist for up to 1 year. Therefore patients receiving measles vaccine should have their antibody status checked.

After injection of immunoglobulin the transitory rise of the various passively transferred antibodies in the patients blood may result in misleading positive results in serological testing.

Passive transmission of antibodies to erythrocyte antigens, e.g. A, B, D may interfere with some serological tests for red cell allo-antibodies (e.g. Coombs test), reticulocyte count and haptoglobin.

4.6 Pregnancy and Lactation

Pregnancy Category C: Animal reproduction studies have not been conducted with ImmunoRel®.It is also not known whether ImmunoRel®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® 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.

Immunoglobulins are excreted into the milk and may contribute to the transfer of protective antibodies to the neonate.

4.7 Effects on Ability to Drive and Use Machines

No effects on ability to drive and use machines have been observed.

4.8 Undesirable Effects

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® although contains small amounts of IgA ≤ 80 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 transferals of blood group e.g., anti-D antibodies.

Rarely human normal immunoglobulins may cause a sudden fall in blood pressure and, in isolated cases, anaphylactic shock,

Thromboembolic events such as myocardial infarction, stroke, pulmonary embolism, deep vein thrombosis have been observed.

Noncardiogenic pulmonary oedema (Transfusion Related Acute Lung Injury, TRALI) have been observed in patients administered IVIG

4.9 Overdose

Overdose may lead to fluid overload and hyperviscosity, particularly in patients at risk,including elderly patients or patients with renal impairment.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties

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 immunoglobulin in immune-mediated disorders.

5.2 Pharmacokinetic Properties

In normal subjects:

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 extravascular (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.

5.3 Preclinical Safety Data

Immunoglobulins are normal constituents of the human body. In animals, acute toxicity testing is of no relevance because of the excessive dose required. Repeated dose toxicity testing and embryo-foetal toxicity studies are impracticable. Effects of the product on the immune system of the newborn have not been studied.

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

Maltose is used as a stabiliser in the concentration of 100g/l.

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products, whole blood and packed red cells.

6.3 Shelf Life

36 months.

6.4 Special Precautions for Storage

Store between 2°C and 8°C. Do not freeze.Discard any unused material or half empty vials.

6.5 Nature and Contents of Containers

The solution is contained in glass bottles stoppered with a rubber bung. The bung is covered with a tamper-evident cap.

6.6 Instructions for Use and Handling and Disposal

Do not use after the expiry date given on the label.

ImmunoRel® should be warmed to room temperature before infusion.

ImmunoRel® is a clear or slightly opalescent and colourless or pale yellow liquid. Do not use solutions which are cloudy or have deposits. This may indicate that the protein is unstable or that the solution has become infected.

Once the infusion container has been penetrated, the contents should be used immediately. Any unused product should be disposed of in accordance with local requirements.

7. MARKETING AUTHORIZATION HOLDER

Reliance Life Sciences Pvt Ltd.

8. MARKETING AUTHORIZATION NUMBER(S)

Since ImmunoRel is blood product and old drug, marketing authorization number would refer to the lic no., KD/8.

9. DATE OF FIRST AUTHORIZATION/ RENEWAL OF AUTHORIZATION

ImmunoRel - 05 May 2005.

10. DATE OF REVISION OF TEXT

9th Aug 2019