Summary of Product Characteristics

1. Name of the medicinal product

Generic Name : Human Normal Immunoglobulin For Intravenous Administration BP 5 %

Brand Name : V-Immune

1.2 Strength: 50g/Lit.

1.3 Pharmaceutical form: Solution for Intravenous Administration

1.4 Pack size: 50 mL and 100 mL

2. QUALITATIVE AND QUANTITATIVES COMPOSITION:

Formulation : V-Immune

(Human Normal Immunoglobulin For Intravenous Administration BP 5 %

Shelf Life: 3 Years (36 Months)

3. PHARMACEUTICAL FORM:

Solution for Intravenous Administration

4. CLINICAL PARTICULARS

4.1 Indications and Usage

- **Primary Immunodeficiency Diseases**
  V-IMMUNE is indicated for the treatment of primary immune deficient states, such as: congenital agammaglobulinemia, common variable immunodeficiency, Wiskott-Aldrich syndrome, and severe combined immune deficiencies.
- **B-cell Chronic Lymphocytic Leukemia (CCL)**
  V-IMMUNE is indicated for prevention of bacterial infections in patient with hypogammaglobulinemia and/or recurrent bacterial infections associated with B-cell Chronic Lymphocytic Leukemia (CLL).
- **Idiopathic Thrombocytopenic Purpura (ITP)**
  V-IMMUNE is indicated when a rapid rise in platelet count is needed to prevent and/or to control bleeding in a patient with Idiopathic Thrombocytopenic Purpura.
- **Kawasaki Syndrome**
  V-IMMUNE is indicated for the prevention of coronary artery aneurysms associated with Kawasaki syndrome.

4.2. Posology and method of administration

Replacement therapy should be commenced and monitored under the supervision of a physician experienced in the treatment of immunodeficiency.

Posology

The dose and dose regimen is dependent on the indication.
In replacement therapy the dose may need to be individualized for each patient depending on the clinical response. Dose based on bodyweight may require adjustment in underweight or overweight patients.
The following dose regimens are given as a guideline.

Replacement therapy in primary immunodeficiency (PID) syndromes
The dose regimen should achieve a trough IgG level (measured before the next infusion) of at least 6 g/l or within the normal reference range for the population age. Three to six months are required after the initiation of therapy for equilibration to occur. The recommended starting dose is 0.4 to 0.8 g/kg body weight (bw) given once, followed by at least 0.2 g/kg bw every 3 to 4 weeks.

The dose required to achieve a trough level of IgG of 6 g/l is of the order of 0.2 to 0.8 g/kg bw/month. The dosage interval when steady state has been reached varies from 3 to 4 weeks.
IgG trough levels should be measured and assessed in conjunction with the incidence of infection. To reduce the rate of bacterial infections, it may be necessary to increase the dosage and aim for higher trough levels.

Secondary immunodeficiencies (as defined in 4.1)

The dose regimen should achieve a trough IgG level (measured before the next infusion) of at least 6 g/l or within the normal reference range for the population age. The recommended dose is 0.2 – 0.4 g/kg bw every three to four weeks.

IgG trough levels should be measured and assessed in conjunction with the incidence of infection. Dose should be adjusted as necessary to achieve optimal protection against infections, an increase may be necessary in patients with persisting infection; a dose decrease can be considered when the patient remains infection free.

Primary immune thrombocytopenia (ITP)

There are two alternative treatment schedules:
- 0.8 to 1g/kg bw given on day 1; this dose may be repeated once within 3 days
- 0.4 g/kg bw given daily for 2 to 5 days. The treatment can be repeated if relapse occurs.

Guillain-Barré syndrome

0.4 g/kg bw/day over 5 days (possible repeat of dosing in case of relapse).

Kawasaki disease

2.0 g/kg bw should be administered as a single dose. Patients should receive concomitant treatment with acetylsalicylic acid.

*Chronic inflammatory demyelinating polyneuropathy (CIDP)**

The recommended starting dose is 2 g/kg bw divided over 2 to 5 consecutive days followed by maintenance doses of 1 g/kg bw over 1 to 2 consecutive days every 3 weeks.
The treatment effect should be evaluated after each cycle; if no treatment effect is seen after 6 months, the treatment should be discontinued.
If the treatment is effective long term treatment should be subject to the physicians discretion based upon the patient response and maintenance response. The dosing and intervals may have to be adapted according to the individual course of the disease.

Multifocal Motor Neuropathy (MMN)

Starting dose: 2 g/kg given over 2-5 consecutive days.
Maintenance dose: 1 g/kg every 2 to 4 weeks or 2 g/kg every 4 to 8 weeks.
The treatment effect should be evaluated after each cycle. If insufficient treatment effect is seen after 6 months, the treatment should be discontinued.
If the treatment is effective, long term treatment should be subject to the physician's discretion based upon the patient response. The dosing and intervals may have to be adapted according to the individual course of the disease.

The dosage recommendations are summarized in the following table:

Indication	**Dose**	**Frequency of injections**
Replacement therapy		
Primary immunodeficiency syndromes (PID)	starting dose: 0.4 - 0.8 g/kg bw	
	maintenance dose: 0.2 - 0.8 g/kg bw	every 3 to 4 weeks to obtain IgG trough levels of at least 6 g/l
Secondary immunodeficiencies (as defined in 4.1)	0.2 - 0.4 g/kg bw	every 3 to 4 weeks to obtain IgG trough levels of at least 6 g/l
Immunomodulation		
Primary immune thrombocytopenia (ITP)	0.8 - 1 g/kg bw or 0.4 g/kg bw/d	on day 1, possibly repeated once within 3 days for 2 to 5 days
Guillain-Barré syndrome	0.4 g/kg bw/d	for 5 days
Kawasaki disease	2 g/kg bw	in one dose in association with acetylsalicylic acid
Chronic inflammatory demyelinating polyneuropathy (CIDP)*	starting dose: 2 g/kg bw maintenance dose: 1 g/kg bw	in divided doses over 2 to 5 days every 3 weeks over 1 to 2 days
Multifocal Motor Neuropathy (MMN)	starting dose : 2 g/kg bw	over 2 to 5 consecutive days

	maintenance dose: 1 g/kg bw or 2 g/kg bw	 every 2 to 4 weeks or every 4 to 8 weeks over 2 to 5 days

*The dose is based on the dose used in the clinical studies conducted with Human Normal Immunoglobulin. The duration of treatment beyond 25 weeks should be subject to the physician's discretion based upon the patient response and maintenance response in the long-term. The dosing and intervals may have to be adapted according to the individual course of the disease.

Paediatric population
The posology in children and adolescents (0-18 years) is not different from that of adults as the posology for each indication is given by body weight and adjusted to the clinical outcome of the above mentioned conditions.

Hepatic impairment
No evidence is available to require a dose adjustment.

Renal impairment
No dose adjustment unless clinically warranted, see section 4.4.

Elderly
No dose adjustment unless clinically warranted, see section 4.4.

Method of administration

For intravenous use.
Human Normal Immunoglobulin should be infused intravenously at an initial infusion rate of 0.3 ml/kg bw/hr for approximately 30 min. If well tolerated (see section 4.4), the rate of administration may gradually be increased to 4.8 ml/kg bw/hr.

In PID patients who have tolerated the infusion rate of 4.8 ml/kg bw/hr well, the rate may be further gradually increased to a maximum of 7.2 ml/kg bw/hr.

If dilution prior to infusion is desired, Human Normal Immunoglobulin may be diluted with 5% glucose solution to a final concentration of 50 mg/ml (5%). For instruction, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance (human immunoglobulins) or to any of the excipients listed in section 6.1 (see also section 4.4).
Patients with selective IgA deficiency who developed antibodies to IgA as administering an IgA- containing product can result in anaphylaxis.
Patients with hyperprolinaemia type I or II.

4.4 Special warnings and precautions for use

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

Certain severe adverse reactions 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.

Certain adverse reactions may occur more frequently:
- in case of high rate of infusion,
- in patients with hypogammaglobulinaemia or agammaglobulinaemia, 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.

Potential complications can often be avoided by ensuring that patients:
- are not sensitive to human normal immunoglobulin by initially infusing the product slowly (0.3 ml/kg bw/hr);
- are carefully monitored for any symptoms throughout the infusion period. In particular, patients naive 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.

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 adverse reaction.

In all patients, IVIg administration requires:
- adequate hydration prior to the initiation of the infusion of IVIg
- monitoring of urine output
- monitoring of serum creatinine levels
- avoidance of concomitant use of loop diuretics (see section 4.5.).

For patients suffering from diabetes mellitus and requiring dilution of Human Normal Immunoglobulin to lower concentrations, the presence of glucose in the recommended diluent should be taken into account.

Hypersensitivity

True hypersensitivity reactions are rare. They can occur in patients with anti-IgA antibodies.

IVIg is not indicated in patients with selective IgA deficiency where the IgA deficiency is the only abnormality of concern.

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

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

implemented. Haemolytic anaemia

IVIg products can contain blood group antibodies which may act as haemolysins and induce in vivo coating of red blood cells (RBC) with immunoglobulin, causing a positive direct antiglobulin reaction (Coombs' test) and, rarely, haemolysis. Haemolytic anaemia can develop subsequent to IVIg therapy due to enhanced RBC sequestration. The Human Normal Immunoglobulin manufacturing process includes an immunoaffinity chromatography (IAC) step that specifically reduces blood group A and B antibodies (isoagglutinins A and B). Clinical data with Human Normal Immunoglobulin manufactured with the IAC step show statistically significant reductions of haemolytic anaemia (see section 4.8, section 5).
Isolated cases of haemolysis-related renal dysfunction/renal failure or disseminated intravascular coagulation and death have occurred.
The following risk factors are associated with the development of haemolysis: high doses, whether given as a single administration or divided over several days; non-O blood group; and underlying inflammatory state. As this event was commonly reported in non-O blood group patients receiving high doses for non-PID indications, increased vigilance is recommended. Haemolysis has rarely been reported in patients given replacement therapy for PID.

IVIg recipients should be monitored for clinical signs and symptoms of haemolysis. If signs and/or symptoms of haemolysis develop during or after an IVIg infusion, discontinuation of the IVIg treatment should be considered by the treating physician (see also section 4.8).

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 bw) 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.

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 based on clinical judgement.

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 case 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 containing various excipients such as sucrose, glucose and maltose, those containing sucrose as a stabiliser accounted for a disproportionate share of the total number. In patients at risk, the use of IVIg products that do not contain sucrose should therefore be considered. Human Normal Immunoglobulin does not contain sucrose, maltose or glucose.
In patients at risk of acute renal failure, IVIg products should be administered at the minimum rate of infusion and dose practicable based on clinical judgement.

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 injection 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

Human Normal Immunoglobulin is made from human plasma. 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) and for the non-enveloped viruses such as hepatitis A virus (HAV) 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.

Sodium content

This medicinal product contains less than 2.3 mg sodium per 100 ml, equivalent to 0.12% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

Paediatric population

Although limited data is available, it is expected that the same warnings, precautions and risk factors apply to the paediatric population. In post marketing reports it is observed that IVIg high-dose indications in children, particularly Kawasaki disease, are associated with an increased reporting rate of haemolytic reactions compared to other IVIg indications in children.

4.5 Interaction with other medicinal products and other forms of interaction

Live attenuated virus vaccines
Immunoglobulin administration may impair for a period of at least 6 weeks and up to 3 months the efficacy of live attenuated virus vaccines such as measles, rubella, mumps, and varicella. After administration of this medicinal 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.

Loop diuretics
Avoidance of concomitant use of loop diuretics.

Paediatric population
Although limited data is available, it is expected that the same interactions may occur in the paediatric population.

4.6 Fertility, pregnancy and lactation

Pregnancy
The safety of this medicinal product for use in human pregnancy has not been established in controlled clinical trials and therefore should only be given with caution to pregnant women and breast-feeding mothers. IVIg products have been shown to cross the placenta, increasingly during the third trimester. Clinical experience with immunoglobulins suggests that no harmful effects on the course of pregnancy, or on the foetus and the neonate are to be expected.
Experimental studies of the excipient L-proline carried out in animals found no direct or indirect toxicity affecting pregnancy, embryonal or foetal development.

Breast-feeding
Immunoglobulins are excreted into the milk and may contribute to protecting the neonate from pathogens which have a mucosal portal of entry.

Fertility
Clinical experience with immunoglobulins suggests that no harmful effects on fertility are to be expected.

4.7 Effects on ability to drive and use machines

Human Normal Immunoglobulin has minor influence on the ability to drive and use machines, e.g. dizziness (see section 4.8). Patients who experience adverse reactions during treatment should wait for these to resolve before driving or operating machines.

4.8 Undesirable effects

Summary of the safety profile
Adverse reactions such as chills, headache, dizziness, fever, vomiting, allergic reactions, nausea, arthralgia, low blood pressure and moderate low back pain may occur occasionally in connection with intravenous administration of human immunoglobulin.

Rarely human normal immunoglobulins may cause a sudden fall in blood pressure and, in isolated cases, anaphylactic shock, even when the patient has shown no hypersensitivity to previous administration.

Cases of reversible aseptic meningitis and rare cases of transient cutaneous reactions (including cutaneous lupus erythematosus – frequency unknown) have been observed with human normal immunoglobulin.

Reversible haemolytic reactions have been observed in patients, especially those with blood

groups A, B, and AB in immunomodulatory treatment. Rarely, haemolytic anaemia requiring transfusion may develop after high dose IVIg treatment (see section 4.4).

Increase in serum creatinine level and/or acute renal failure have been observed.

Very rarely: Transfusion related acute lung injury (TRALI) and thromboembolic reactions such as myocardial infarction, stroke, pulmonary embolism and deep vein thromboses.

Tabulated list of adverse reactions
Seven clinical studies were performed with Human Normal Immunoglobulin, which included patients with PID, ITP and CIDP. In the pivotal PID study, 80 patients were enrolled and treated with Human Normal Immunoglobulin. Of these,
72 completed the 12 months of treatment. In the PID extension study, 55 patients were enrolled and treated with Human Normal Immunoglobulin. Another clinical study included 11 PID patients in Japan. Two ITP studies were performed with 57 patients each. Two CIDP studies were performed with 28 and 207 patients, respectively.

Most adverse drug reactions (ADRs) observed in the seven clinical studies were mild to moderate in nature.

The following table shows an overview of the ADRs observed in the seven clinical studies categorized according the MedDRA System Organ Class (SOC), Preferred Term Level (PT) and frequency.
Frequencies were evaluated according to the following conventions: Very common (≥1/10), Common (≥1/100 to <1/10), Uncommon (≥1/1,000 to <1/100), Rare (≥1/10,000 to <1/1,000), Very rare (<1/10,000). For spontaneous post-marketing ADRs, the reporting frequency is categorized as unknown.
Within each frequency grouping, undesirable effects are presented in order of decreasing frequency.

MedDRA System Organ Class (SOC)	**Adverse Reaction**	**Frequency per patient**	**Frequency per infusion**
Infections and infestations	Aseptic meningitis	Uncommon	Rare
MedDRA System Organ Class (SOC)	**Adverse Reaction**	**Frequency per patient**	**Frequency per infusion**
Blood and lymphatic system disorders	Anaemia, haemolysis (including haemolytic anaemia)[β], leukopenia	Common	Uncommon
	Anisocytosis (including microcytosis)	Uncommon	Uncommon
	Thrombocytosis		Rare
	Decreased neutrophil count	Unknown	Unknown
Immune system disorders	Hypersensitivity	Common	Uncommon
	Anaphylactic shock	Unknown	Unknown
Nervous system disorders	Headache (including sinus headache, migraine, head discomfort, tension headache)	Very common	Very common

	Dizziness (including vertigo)	Common	Uncommon
	Somnolence	Uncommon	Uncommon
	Tremor		Rare
Cardiac disorders	Palpitations, tachycardia	Uncommon	Rare
Vascular disorders	Hypertension, flushing (including hot flush, hyperaemia)	Common	Uncommon
	Hypotension		Rare
	Thromboembolic events, vasculitis (including peripheral vascular disorder)	Uncommon	Rare
	Transfusion related acute lung injury	Unknown	Unknown
Respiratory, thoracic and mediastinal disorders	Dyspnoea (including chest pain, chest discomfort, painful respiration)	Common	Uncommon
Gastrointestinal disorders	Nausea, vomiting, diarrhoea	Common	Common
	Abdominal pain		Uncommon
Hepatobiliary disorders	Hyperbilirubinaemia	Common	Rare
Skin and subcutaneous tissue disorders	Skin disorder (including rash, pruritus, urticaria, maculo-papular rash, erythema, skin exfoliation)	Common	Common
Musculoskeletal and connective tissue disorders	Myalgia (including muscle spasms, musculoskeletal stiffness, musculoskeletal pain)	Common	Uncommon
Renal and urinary disorders	Proteinuria, increased blood creatinine	Uncommon	Rare
	Acute renal failure	Unknown	Unknown
General disorders and administration site conditions	Pain (including back pain, pain in extremity, arthralgia, neck pain, facial pain) pyrexia (including chills), influenza like illness (including nasopharyngitis, pharyngolaryngeal pain, oropharyngeal blistering, throat tightness)	Very common	Common
	Fatigue	Common	Common
	Asthenia (including muscular weakness)		Uncommon
	Injection site pain (including infusion site discomfort)	Uncommon	Rare
Investigations	Decreased haemoglobin (including decreased red blood cell count, decreased haematocrit), Coombs`	Common	Uncommon

MedDRA System Organ Class (SOC)	Adverse Reaction	Frequency per patient	Frequency per infusion
	(direct) test positive, increased alanine aminotransferase, increased aspartate aminotransferase, increased blood lactate dehydrogenase		

β The frequency is calculated based on studies completed prior to implementation of the Immunoaffinity Chromatography isoagglutinin reduction step (IAC) into Human Normal Immunoglobulin production. In a Post-Authorization Safety Study (PASS): "Human Normal Immunoglobulin Use and Haemolytic Anaemia in Adults and Children and the Human Normal Immunoglobulin Safety Profile in Children with CIDP – An Observational Hospital-Based Cohort Study in the US", assessing data of 7,759 patients who received Human Normal Immunoglobulin identifying 4 haemolytic anaemia cases after IAC versus 9,439 patients who received Human Normal Immunoglobulin identifying 47 haemolytic anaemia cases prior to IAC (baseline), an 89% statistically significant reduction in the overall rate of probable haemolytic anaemia was demonstrated based on an incidence rate ratio of 0.11 adjusted for in-/outpatient setting, age, sex, Human Normal Immunoglobulin dose and indication for Human Normal Immunoglobulin use (one- sided p-value <0.01). Probable cases of haemolytic anaemia were defined by an International Classification of Disease (ICD)-9 or ICD-10 hospital discharge code specific for haemolytic anaemia. Possible cases of haemolytic anaemia consisted of an unspecified transfusion reaction identified via ICD-9 or ICD-10 discharge codes or via review of hospital charge descriptions in temporal association with a haptoglobin, a direct antiglobulin test or indirect antiglobulin performed in the workup of haemolytic anaemia.

For safety with respect to transmissible agents and additional details on risk factors, see section 4.4.

Paediatric Population

In Human Normal Immunoglobulin clinical studies with paediatric patients, the frequency, nature and severity of adverse reactions did not differ between children and adults. In post marketing reports it is observed that the proportion of haemolysis cases to all case reports occurring in children is slightly higher than in adults. Please refer to section 4.4 for details on risk factors and monitoring recommendations.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.

4.9 Overdose

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

5. PHARMACOLOGICAL PROPERTIES:

5.1 Pharmacodynamic properties:

Pharmacotherapeutic group: immune sera and immunoglobulins: immunoglobulins, normal human, for intravascular administration, ATC code: J06BA02.

Human normal immunoglobulin contains mainly immunoglobulin G (IgG) with a broad spectrum of antibodies against infectious agents.

Human normal immunoglobulin contains the IgG antibodies present in the normal population. It is usually prepared from pooled plasma from not fewer than 1,000 donors. It has a distribution of immunoglobulin G subclasses closely proportional to that in native human plasma. Adequate doses of this medicinal product may restore abnormally low immunoglobulin G levels to the normal range and thus help against infections.
The mechanism of action in indications other than replacement therapy is not fully elucidated, but includes immunomodulatory effects.

The safety and efficacy of Human Normal Immunoglobulin was evaluated in 7 prospective, open-label, single-arm, multicenter studies performed in Europe (ITP, PID and CIDP studies), Japan (PID and CIDP studies), and the US (PID and CIDP studies).
Additional safety data were collected in a Post-Authorization Safety Study (PASS), an observational multicentre trial in patients with various immunological conditions performed in the US.

<u>PID</u>
The PID pivotal study included a total of 80 patients aged between 3 and 69 years old. 19 children (3 to 11 years), 12 adolescents (12 to 16 years) and 49 adults were treated with Human Normal Immunoglobulin over 12 months. 1038 infusions were administered, 272 (in 16 patients) in the 3-week schedule and 766 (in 64 patients) in the 4-week schedule. The median doses administered for the 3-week and 4-week treatment schedules were almost identical to each other (428.3 vs. 440.6 mg IgG/ kg bw).The PID extension study included a total of 55 patients aged between 4 and 81 years old. 13 children (3 to 11 years), 8 adolescents (12 to 15 years) and 34 adults were treated with Human Normal Immunoglobulin over 29 months. 771 infusions were administered and the median dose administered was 492.3 mg IgG/kg bw.

<u>ITP</u>
In the ITP pivotal study, in total 57 patients aged between 15 and 69 years old were treated with

2 infusions of Human Normal Immunoglobulin for a total of 114 infusions. The scheduled dose of 1 g/kg bw per infusion was closely adhered to in all patients (median 2 g IgG/kg bw).

In the second ITP study, 57 patients with ITP (baseline platelet counts ≤ 30×10^9/l) aged between 18 and 65 years were treated with Human Normal Immunoglobulin at 1 g/kg bw. On day 3 patients could receive a second dose of 1 g/kg bw, for patients with a platelet count of < 50×10^9/l on day 3 this second dose was mandatory.
Overall, in 42 subjects (74%) the platelet count increased at least once to ≥ 50×10^9/l within 6 days after the first infusion, which was well within the expected range. A second dose in subjects with platelet counts ≥ 50×10^9/l after the first dose provided a relevant additional benefit in terms of higher and longer-lasting increases in platelet counts compared to a single dose. In subjects with platelet counts < 50×10^9/l after the first dose, 30% showed a platelet response of ≥ 50×10^9/l after the mandatory second dose.

CIDP

In the first CIDP study, a prospective multicenter open label trial (Human Normal Immunoglobulin impact on mobility and autonomy PRIMA study), 28 patients (13 subjects who have previously received IVIG and 15 subjects not) were treated with a Human Normal Immunoglobulin loading dose of 2g/kg bw given over 2-5 days followed by 6 maintenance doses of 1g/kg bw over 1-2 days every three weeks. Previously treated patients were withdrawn from IVIG until confirmed deterioration before start of Human Normal Immunoglobulin. On the adjusted 10 point INCAT (Inflammatory Neuropathy Cause and Treatment) scale a clinically meaningful improvement of at least 1-point from baseline to treatment week 25 was observed in 17 out of 28 patients. The INCAT responder rate was 60.7% (95% confidence interval [42.41, 76.4]). 9 patients responded after receiving the initial induction dose by week 4, 16 patients responded by week 10.

Muscle strength as measured by the MRC (Medical Research Council) Score improved in all patients by 6.9 points (95% confidence interval [4.11, 9.75], in previously treated patients by 6.1 points (95% confidence interval [2.72, 9.44]) and in untreated patients by 7.7 points (95% confidence interval [2.89, 12.44]). The MRC responder rate, an increase of at least 3 points, was 84.8% which was similar in previously treated (81.5% [58.95, 100.00]) and untreated (86.7% [69.46, 100.00]) patients.

In patients defined as INCAT non-responders, muscle strength improved by 5.5 points (95% confidence interval [0.6, 10.2]) as compared to INCAT responders (7.4 points (95% confidence interval [4.0, 11.7])

In a second prospective, multicenter randomized, placebo-controlled clinical study

(Polyneuropathy and Treatment with Hizentra, PATH trial), 207 subjects with CIDP were treated with Human Normal Immunoglobulin in the prerandomization phase of the study. Subjects all with IVIg pretreatment of at least 8 weeks and with an IVIg-dependence confirmed by clinically evident deterioration during an IVIg withdrawal phase of up to 12 weeks, received a Human Normal Immunoglobulin loading dose of 2 g/kg bw followed by up to 4 Human Normal Immunoglobulin maintenance doses of 1 g/kg bw every 3 weeks for up to 13 weeks.
Following clinical deterioration during IVIg withdrawal, clinical improvement of CIDP was primarily defined by a decrease of ≥ 1 point at the adjusted INCAT score. Additional measures of CIDP improvement were an increase in R-ODS (Rasch-built Overall Disability Scale) score of ≥ 4 points, a mean grip strength increase of ≥ 8 kPa, or an MRC sum score increase of ≥ 3 points. Overall, 91 % of subjects (188 patients) showed improvement in at least one of the criteria above by week 13.
By adjusted INCAT score, the responder rate by week 13 was 72.9 % (151/207 patients), with 149 patients responding already by week 10. A total of 43 of the 207 patients achieved a better CIDP status as assessed by the adjusted INCAT score compared to their CIDP status at study entry.

The mean improvement at the end of the treatment period compared to reference visit was 1.4 points in the PRIMA (1.8 points in IVIg pretreated subjects) and 1.2 points in PATH study.

In PRIMA, the percentage of responders in the overall Medical Research Council (MRC) score (defined as an increase by ≥ 3 points) was 85 % (87 % in the IVIg-untreated and 82 % in IVIg- pretreated) and 57 % in PATH. The overall median time to first MRC sum score response in PRIMA was 6 weeks (6 weeks in the IVIg-untreated and 3 weeks in the IVIg-pretreated) and 9.3 weeks in PATH. MRC sum score in PRIMA improved by 6.9 points (7.7 points for IVIg-untreated and points for IVIg-pretreated) and by 3.6 points in PATH.
The grip strength of the dominant hand improved by 14.1 kPa (17.0 kPa in IVIg-untreated and 10.8 kPa in IVIg pretreated subjects) in the PRIMA study, while in PATH the grip strength of the dominant hand improved by 12.2 kPa. For the non dominant hand similar results were observed in both PRIMA and PATH trials.

The efficacy and safety profile in the PRIMA and the PATH study in CIDP patients were overall comparable.

Post-Authorisation Safety Study (PASS)

In an observational hospital-based cohort Post-Authorisation Safety Study (PASS), the risk of haemolytic anaemia following Human Normal Immunoglobulin therapy was evaluated in patients with various immunological conditions from 1 January 2008 to 30 April 2019. The risk of haemolytic anaemia was assessed prior (baseline) and after the implementation of a risk minimisation measure, the introduction of the Immunoaffinity Chromatography (IAC) step in the Human Normal Immunoglobulin manufacturing process. Probable cases of haemolytic anaemia were defined by an ICD-9 or ICD-10 hospital discharge code specific for haemolytic anaemia. (Possible cases of haemolytic anaemia consisted of an unspecified transfusion reaction identified via ICD-9 or ICD-10 discharge codes or via review of hospital charge descriptions in temporal association with a haptoglobin, a direct antiglobulin test or indirect antiglobulin performed in the workup of haemolytic anaemia).

A statistically significant rate reduction of 89% of haemolytic anaemia (based on an incidence rate ratio of 0.11; adjusted for in-/outpatient setting, age, sex, Human Normal Immunoglobulin dose and indication for Human Normal Immunoglobulin use; one-sided p-value <0.01) was observed after implementation of the IAC step compared to baseline:

	Baseline	**IAC**
Period[ϕ]	1. January 2008- 31. December 2012	1. October 2016- 30. April 2019
Median anti-A titers[£]	1:32	1:8
Median anti-B titers[£]	1:16	1:4
Probable haemolytic anaemia[α] cases	47	4
Patient number (n)	n=9439	n=7759
Crude incidence rate of probable haemolytic anaemia [α] per 10.000 patient-days at risk	0.74 95% CI[&]: 0.54-0.98	0.08 95% CI: 0.02-0.20
Incidence rate reduction of probable haemolytic anaemia [α] versus baseline	-	89%
Adjusted[7] incidence rate ratio for haemolytic anaemia versus baseline	-	0.11 95% CI: 0.04-0.31, one-sided p-value: <0.01

[ϕ] The exclusion of human blood plasma donors with high anti-A titres performed between 1. October 2013 and 31. December 2015 as the initial risk minimisation measure for haemolytic anaemia indicated a 38% reduction in probable haemolytic anaemia incidence versus baseline and was subsequently replaced by the IAC step in the Human Normal Immunoglobulin manufacturing process, as provided above.

[£] Median isoagglutinin titers measured by direct testing method according to Ph.Eur

[α] Probable haemolytic anaemia case: defined by an ICD-9 or ICD-10 hospital discharge code specific for haemolytic anaemia and the occurrence during the time interval from the first infusion up to 30 days after the last infusion, if >1 Human Normal Immunoglobulin infusions were administered.

[&] Confidence interval

[7] Adjusted for: in-/outpatient setting, age, sex, Human Normal Immunoglobulin dose and indication for Human Normal Immunoglobulin use

The reduction in probable haemolytic anaemia incidence rate after IAC implementation versus baseline was especially pronounced in patients treated with Human Normal Immunoglobulin doses ≥0.75 g/kg bw.

Additionally, 28 paediatric patients with CIDP <18 years of age were identified throughout the entire study period from 1 January 2008 to 30 April 2019. No paediatric patients with CIDP given a total of 486 Human Normal Immunoglobulin administrations experienced haemolytic anaemia, AMS, acute renal failure, severe anaphylactic reaction or a thromboembolic event. Two patients experienced a moderate anaphylactic reaction, equating to 0.4% of all Human Normal Immunoglobulin administrations.

Paediatric population
No differences were observed in the pharmacodynamic properties and safety profile between adult and paediatric study patients.

5.2 Pharmacokinetics

Absorption
Human normal immunoglobulin is immediately and completely bioavailable in the recipient's circulation after intravenous administration.

Distribution
It is distributed relatively rapidly between plasma and extravascular fluid, after approximately 3-5 days equilibrium is reached between the intra- and extravascular compartments.

Elimination
IgG and IgG complexes are broken down in the cells of the reticuloendothelial system. The half-life may vary from patient to patient. The pharmacokinetic parameters for Human Normal Immunoglobulin were determined in a clinical study in PID patients (see section 5.1). 25 patients (aged 13-69 years) participated in the pharmacokinetic (PK) assessment. In this study, the median half-life of Human Normal Immunoglobulin in PID patients was
36.6 days. In an extension of this study, 13 PID patients (aged 3-65 years) participated in a PK sub- study. The results of this study show the median half-life of Human Normal Immunoglobulin to be 31.1 days (see table below).

Pharmacokinetic parameters of Human Normal Immunoglobulin in PID patients

Parameter	Pivotal Study (N=25) ZLB03_002CR Median (Range)	Extension Study (N=13) ZLB05_006CR Median (Range)
C_{max} (peak, g/l)	23.4 (10.4-34.6)	26.3 (20.9-32.9)
C_{min} (trough, g/l)	10.2 (5.8-14.7)	12.3 (10.4-18.8) (3-week schedule) 9.4 (7.3-13.2) (4-week schedule)
t½ (days)	36.6 (20.6-96.6)	31.1 (14.6-43.6)

C_{max}, maximum serum concentration; C_{min}, trough (minimum level) serum concentration; t½, elimination half-life

Paediatric population
No differences were seen in the pharmacokinetic parameters between adult and paediatric study patients with PID. There are no data on pharmacokinetic properties in paediatric patients with CIDP.

5.3 Preclinical safety Data:

Immunoglobulins are a normal constituent of the human body. L-proline is a physiological, non-essential amino acid.

The safety of Human Normal Immunoglobulin has been assessed in several preclinical studies, with particular reference to the excipient L-proline. Some published studies pertaining to hyperprolinaemia have shown that long- term, high doses of L-proline have effects on brain development in very young rats. However, in studies where the dosing was designed to reflect the clinical indications for Human Normal Immunoglobulin, no effects on brain development were observed. Non-clinical data reveal no special risk for humans based on safety pharmacology and toxicity studies.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients:
Maltose and water for Injection

6.2 Incompatibilities:
This medicinal product must not be mixed with other medicinal products.

6.3 Shelf life:
3 years (36 Months).

6.4 Special precautions for storage:
Store at 2-8°C. Do not freeze. Protect from light. Keep out of reach and sight of children.

6.5 Nature and contents of container:
Human Normal Immunoglobulin for intravenous use 5% is supplied in USP type I glass vials, stoppered with rubber stoppers/rubber closures/ Elastomeric rubber closures and sealed with Mist Grey color aluminum flip-off seals.

6.6. Special precautions for disposal

Human Normal Immunoglobulin comes as a ready-to-use solution in single-use vials. The product should be brought to room temperature (25 °C) before use. A vented infusion line should be used for the administration of Human Normal Immunoglobulin. Flushing of the infusion tubes with physiological saline or 5% glucose solution is permitted. Always pierce the stopper at its centre, within the marked area.

The solution should be clear or slightly opalescent and colourless or pale yellow. Solutions that are cloudy or have deposits should not be used.
If dilution is desired, 5% glucose solution should be used. For obtaining an immunoglobulin solution of 50 mg/ml (5%), Human Normal Immunoglobulin 100 mg/ml (10%) should be diluted with an equal volume of the 5% glucose solution. Aseptic technique must be strictly observed during the dilution of Human Normal Immunoglobulin.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

6.7 Pack size: 50 mL and 100 mL

7. MARKETING AUTHORIZATION HOLDERS

Name	:	VIRCHOW HEALTHCARE PRIVATE LIMITED
Address	:	901, DLH Park, S.V. Road, Goregaon (West), Mumbai – 400062. INDIA
Tel.	:	91 22 28795600/53
Fax	:	91 22 28724855
Email	:	regulatorymgr@virchowhealthcare.com

8.MARKETING AUTHORIZATION NUMBER

NA

9.DATE OF FIRST AUTHORIZATION/ RENEWAL OF THE AUTHORIZATION

Not Applicable

10.DATE OF REVISION OF THE TEXT

Not Applicable

11.NAME AND ADDRESS OF THE MANUFACTURE

Name	:	Virchow Biotech Pvt. Ltd.
Address	:	Survey No.172 Part, Gagillapur(V), Dundigal Gandimaisamma (M), Medchal- Malkajgiri (D), Telangana-500043, India
Tel.	**:**	91 22 28795600/653
Fax	:	91 22 28795699
E-mail	**:**	regulatory.vbpl@gmail.com