Overview Study on Intravenous Immunoglobulin and Global Market Scenario of IVIG

By

Ankit Khandelwal

Dissertation submitted for the partial fulfillment of the

MBA Pharmaceutical Management

Academic year, 2016-2018

The IIHMR University, Jaipur

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INSTITUTE OF HEALTH
MANAGEMENT RESEARCH
(WHO Collaborating Centre for District Health System Based on Primary Health Care)

IIHMR UNIVERSITY

TO WHOMSOEVER MAY CONCERN

This is to certify that **Ankit Khandelwal** student of MBA Pharmaceutical Management from The IIHMR University, Jaipur has undergone Dissertation training at **PlasmaGen BioSciences Pvt. Ltd.**, Bangalore from 5th February to 4th May 2018

The Candidate has successfully carried out the study designated to him during internship training and his approach to the study has been sincere, scientific and analytical.

The Internship is in fulfillment of the course requirements.

I wish him all success in all his future endeavors.

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PlasmaGen Biosciences

15th May,2018

To whomsoever concerned

This is to certify that **Mr. Ankit Khandelwal** (Employee code – 347) working with PlasmaGen Biosciences (P) Ltd as Executive – Sales & Marketing, has successfully completed his dissertation on the topic **"An Overview Study of Intravenous Immunoglobulin and Global Market Scenario of IVIG"** during the period 5th February, 2018 to 4th May, 2018 under the supervision of Mr. Anant Bharne (GM – Sales & Marketing), Mr. Rakin Khan (Product Management Executive) and Ms. Payal Shobhwani (Product Executive).

For PlasmaGen Biosciences (P) Ltd.,

15/05

M/s. PlasmaGen Biosciences Pvt. Ltd. BANGALORE-18

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CERTIFICATE BY SCHOLAR

This is to certify that the dissertation titled **"An overview study of Intravenous Immunoglobulin and global market scenario of IVIG"** and submitted by **Ankit Khandelwal Enrollment No.**0060 under the supervision of Mr. Rahul Sharma for award of MBA in Pharmaceutical Management of the University carried out during the period from 5th February to 4th May embodies my original work and has not formed the basis for the award of any degree, diploma associate ship, fellowship, titles in this or any other institute or other similar institution of higher learning.

Ankit Khandelwal

Signature

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First and foremost, I venerate to the God whose mercy, compassion and benediction have guided me in each step during the course of my life and this study as well.

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Ankit Khandelwal

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Abbreviations

SAARC	South Asian Association for Regional Co-operation
CDSCO	Central Drug and Standard Control Organization
DGFT	Director General of Foreign Trade
DIC	Disseminated Intravascular Coagulation
FFP	Fresh Frozen Plasma
GBS	Guillain Bare Syndrome
HSA	Human Serum Albumin
IPPC	International Plasma Protein Congress
ITP	Idiopathic Thrombocytopenia Purpura
IVIg	Intravenous Immunoglobulin
MRB	Market Research Bureau
NACO	National AIDS Control Organization
NIB	National Institute of Biologicals
PCV	Packed Cell Volume
PPTA	Plasma Protein Therapeutic Association
SCID	Severe Combined Immunodeficiency
VWF	Von Willebrand Factor
WFH	World Federation of Hemophilia
CIDP	Chronic inflammatory demyelinating polyneuropathy
USFDA	United State Food and Drug Administration
HIV	Human immunodeficiency virus

Executive Summary

The scope of application of IVIG has widened as it is used to treat various neurological, hematological, dermatological, and immune deficiency disorders, with the help of improved clinical practices and advanced technologies. IVIG is considered to be the most effective treatment for Hypogammaglobulinemia, CIDP, and Immunodeficiency diseases. The products gained significant attention in the recent years due to their high efficacy in the treatment of immune diseases .

IVIG is extensively used for the treatment of immune disorders. USFAD and EMA have approved the use of IVIG for indications namely CIDP, ITP, Primary Immunodeficiency Diseases (PID), Secondary Immunodeficiency in Chronic Lymphocytic Leukemia, Pediatric human immunodeficiency virus (HIV) infection, Kawasaki disease, Specific antibody Deficiency, Acquired Hypogammaglobulinemia, Myasthenia Gravis, and others .

Currently, Hypogammaglobulinemia, CIDP and immunodeficiency diseases are the largest revenue-generating segments in the global IVIG market contributing for ~58% of the revenue in the market. Hypogammaglobulinemia application accounted for $ 1,720.5 million in 2015 and is expected to reach $2,634.2 million by 2022, growing at a CAGR of 6.4%, during the analysis period of 2016–2022 .

Some of the leading global companies profiled in this report include CSL Behring, Baxter International Inc., Grifols Worldwide, Biotest Ag, Kedrion Biopharma, Octapharma Ag, LFB group, and China Biologic Products Inc., BDI pharma, and Bayer Healthcare**. Indian Company like Reliance Life Sciences, Intas Pharmaceuticals Ltd., PlasmaGen BioSciences, Wockhardt Limited now focuses on the development of IVIG products.**

The project assigned was An overview study of IntravenousImmunoglobulin and Global market scenario of IVIG objective being**:**

- ✓ To understand the wide usage of IVIG in different indications.
- ✓ To understand the global market of IVIG.
- ✓ To determine the market share of different brands of medicine Available in market.
- ✓ To understand the global market trends of IVIG

Company Profile

Who PlasmaGen BioSciences are:

PlasmaGen BioSciences is an Indian Bio-pharmaceutical organization specializing exclusively in Plasma Protein Therapy. We therefore pursue a vision of ushering in the Plasma Protein industry in SAARC region & endeavor to provide an extensive assortment of safe plasma products to enrich the quality of life of patients. This is a step working towards addressing the very contemporary concept of regional self-sufficiency .

PlasmaGen BioSciences, having a niche and expertise in the cosmos of plasma product therapies; also works closely with the government on various plasma policies and haemovigilance, which can be extended and leveraged for growth of this industry in entire SAARC region .

PlasmaGen BioSciences was established in the year 2010 on September 7th. Headquartered in Bangalore- India, PlasmaGen has been making every effort in the domain of Plasma Product Industry and has become an Imperative one stop destination for the medical fraternity for most of the plasma products need .

Plasmagen has a basket of plasma products and the widest range of immunoglobulins in India catering to the requisites of various realms viz. Hematology, Oncology, Immunology, Pediatrics, Rheumatology, Dermatology and Neurology .

South Asian Association for Regional Co-operation (SAARC) includes 8 countries; India, Afghanistan, Bangladesh, Bhutan, Maldives, Nepal, Pakistan and Sri Lanka, these countries not only share geographical proximity and political agenda but also share many common social concerns- Healthcare, Education, Economic Infrastructure and many more .

What PlasmaGen BioSciences do:

Plasma Collection: we source the recover plasma, through a network of licensed Blood banks spreads across the country, which undergoes series of extensive audits before collections, in orders to meet the pre –requisite criteria. It is noteworthy to mention that plasmaGen is one of the very few companies in India who has been granted the licensed from drug controller general of india (DCGI) to collect recover plasma .

Plasma Management:

PlasmaGen BioSciences take care of the logistics involved in Plasma handling, once it is procured from the respective blood bank centers.
In a country like India; which experiences extreme temperatures variations, the task of maintaining critical temperatures& stringent conditionsof plasma in transition becomes quite challenging .

Our well trained and dedicated team for Plasma sourcing and management ensures that each unit is packaged and shipped under strictly controlled environmental conditions & prudently executes end to end cold chain transfer to our storage facility .

Our PlasmaGen Biosciences Technology Centre located in Bangalore houses a state of art licensed cold storage facility of capacity of up to 60,000 liters annually.

Manufacturing of Plasma product:

PlasmaGen BioSciences established its own manufacturing facility in Bangalore, India. This facility aims at quadrupling the existing capacity in the near future.

Products of PlasmaGen BioSciences:

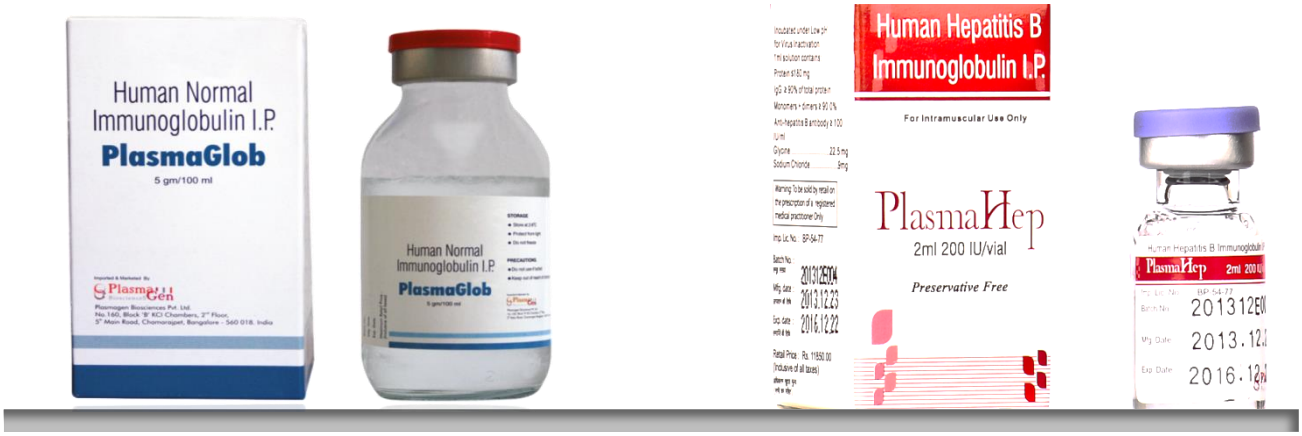

Figure 1 Plasma journey of plasmaGen Product


Pristine Quality
Spotless Delivery
O
A
B
AB
Blood Bank
Plasma is procured from Licensed Blood Banks after conducting series of extensive Audits.
Each bag is tested for 5 viral markers viz.
Hepatitis B
Hepatitis C
H.I.V.
Malaria
Syphilis
By highly sensitive techniques such as NAT or ELISA.
Cold chain transport ≤-20°C.
≤-20°C
≤-20°C
Procured plasma is stored at ≤-20°C.
Maintenance of vein to bag backtracking registry at PlasmaGen BioSciences storage center.
Products tested and approved at NIB.
TESTED APPROVED
PlasmaGlob
HUMAN ALBUMIN I.P.
BumiNext
Final product tested at the manufacturing site for 3 viral markers viz.
Hepatitis B
Hepatitis C
H.I.V.
Purification Process:
Viral Inactivation
&
Viral Removal
Mini pool testing
Manufacturing pool testing
TESTED APPROVED
Plasma pool tested and approved at NIB.

Introduction

plasma products have shown a tremendous growth over the past year. Although discovery of recombinant Product has challenged naturally derived plasma protein preparation but still In developing country like India. Plasma product are gaining popularity due to their higher acceptability by elder population .

Reason for growth of plasma product are due to uses in new indication, Higher-purification, Growing concern among Indian biopharmaceutical industry like Reliance, Intas, Bharat serum, etc. Hence lots of biopharmaceutical companies are entering into this segment and for effective lunching of their product and gaining the maximum market share, marketers are trying to identify the prescribing habits and pattern of doctors .

Composition of Blood

Blood is a liquid, contained within blood vessels. Its major functions are to supply nutrients (such as oxygen, glucose, vitamins and minerals) to other tissues, to transport waste products (such as carbon dioxide and lactic acid), to protect the body from invasion by foreign organisms and to recognize and reject foreign tissues .

Blood also functions as a regulator of body temperature. The cellular components of blood are red blood cells, white blood cells, and platelets and the liquid component of the blood is called as the plasma. When the blood present in the testube already containing the anticoagulant is centrifuged the plasma and the blood cells separates .

Erythrocytes normally constitute about 45% of the total volume of a blood sample, a percentage known as the hematocrit (he-mato-krit; “blood fraction”). Normal hematocrit values vary. In healthy males the norm is 47% 5%; in females it is 42% 5%. Leukocytes and platelets contribute less than 1% of blood volume. Plasma makes up most of the remaining 55% of whole blood .

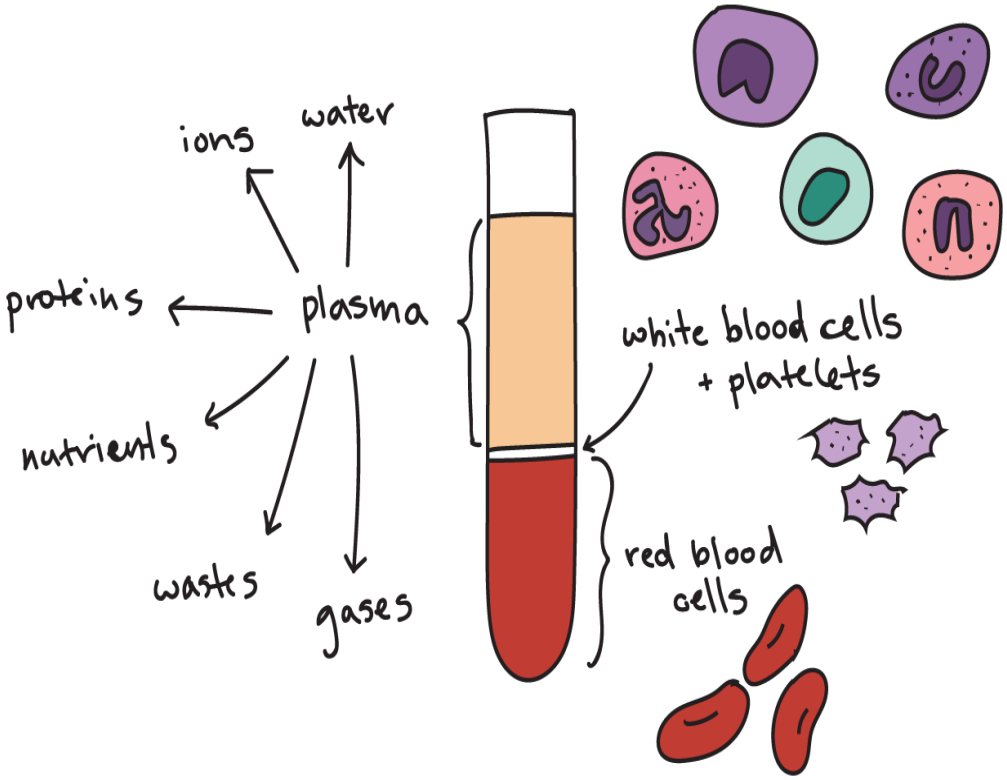

Figure 2 Composition of blood

The blood of cells is dividing into three groups:

1. Erythrocytes – Red blood cells
2. Leukocytes – White blood cells
3. Thrombocytes – Platelets

Plasma

Plasma is the pale yellow colored liquid component of blood. It is Newtonian in nature with viscosity close to water. It mostly consists of water (up to 95% by volume), various biochemicals such as enzymes, lipids and hormones, a wide range of proteins in dissolved state such as immunoglobulins, transport proteins, lipoproteins, complement factors, coagulation factors and proteinase inhibitors, as well as many gases in dissolved state .

Components	Percentage
Water	~90
Protein	7.1
Salt	0.9
Lipid	1.9
Blood Sugar	0.1

Table 1 : Components of Plasma

Type of Plasma:

Human plasma for fractionation may be obtained may be separation from whole blood or directly by a plasmapheresis route.

1. Recovered Plasma
2. Source Plasma

1. **Recovered Plasma:** It is recovered from blood donated by voluntary non – remunerated donors at blood center. The blood is collected, and plasma is separated from whole blood by centrifugation as per national regulatory guidelines of the country. The cellular components of the blood are utilized for clinical purpose, while plasma is frozen for further use. It can either be used for clinical purpose or for fractionation .

2. **Source Plasma:** It is obtained by a process called plasmapheresis, where only the plasma is collected from the donor, while the cellular components are returned back to the donor through a closed system in the same cycle. Globally, most of the source plasma is collected from voluntary but remunerated donors .

- ***Hyperimmune Plasma:*** This plasma is collected from a group of selected donors, who have a higher titer level of the specific antibodies. This specialized plasma can be used to extract particular hyperimmune globulins such as Anti – D immune globulin, Hepatitis B immune globulin & Rabies immune globulin .

Classification of Plasma proteins

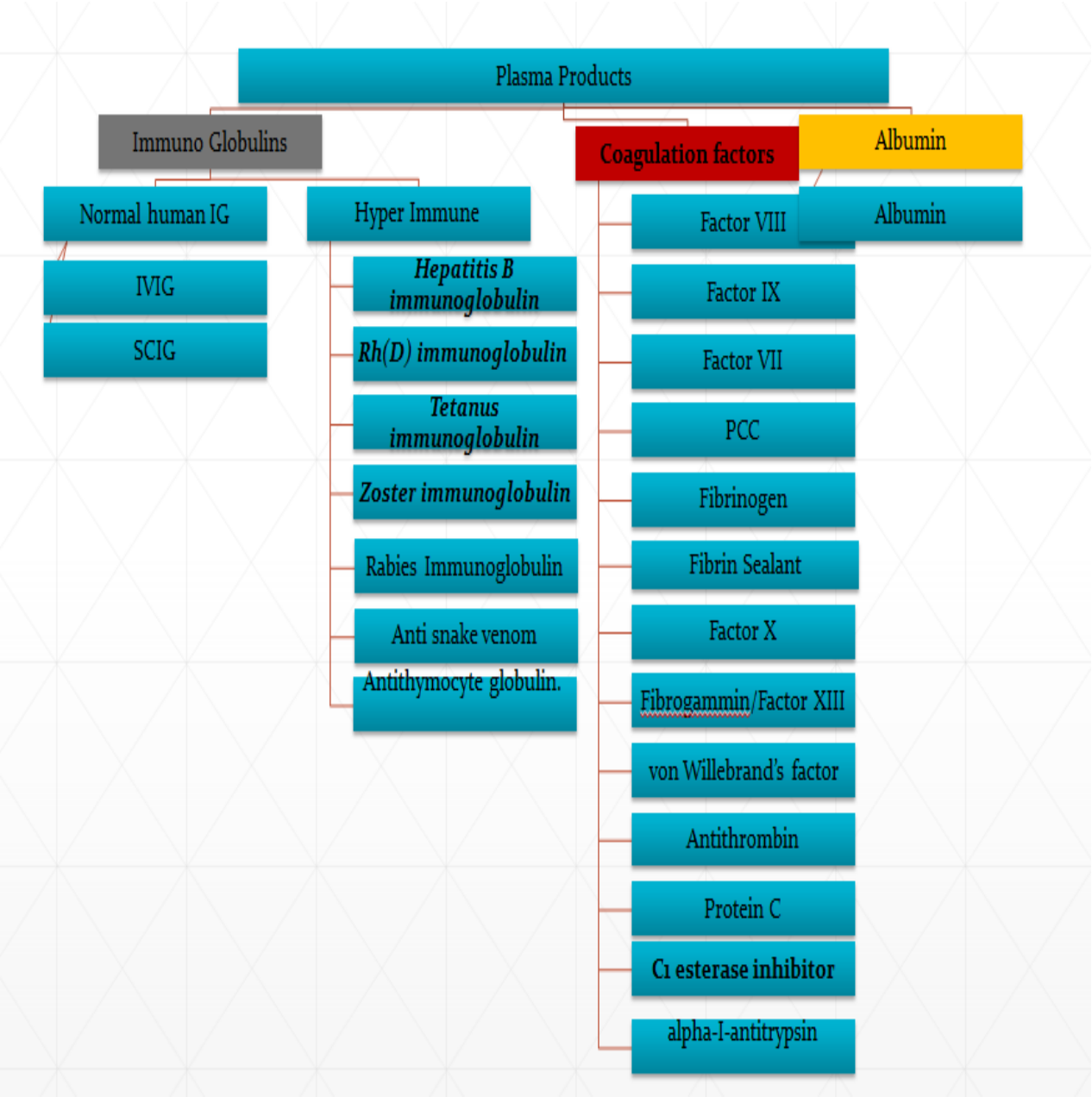

Figure 3 Classification of Plasma Protein

Immunoglobulins:

Immunoglobulins are produced by B cells (antibodies) in response to an immunogen and are among the most abundant proteins in the blood, comprising 20% (by weight) of total plasma proteins.

Albumin is the major protein component, with the immunoglobulins being within the four other more positively charged peaks, particularly in the gamma globulin area. Immunoglobulin Structure There are five classes of immunoglobulins, all of which share the same fundamental structure (Fig. 2). Resembling the letter Y, the basic structure is composed of two heavy chains and two light chains held together by interchain disulfide bonds. This monomeric unit has a molecular weight of about 150,000 (heavy chains of 50,000 each and light chains of 25,000 each) .

An antibody is an immunoglobulin with specificity for a particular antigen. Antibody production is critical for preventing and limiting the course of infectious disease. Each chain of the immunoglobulin molecule has a series of intrachain loops of about 90 amino acids that are held together by intrachain disulfide bonds. In the example above, each light chain has two domains, while the heavy chains have four domains .

BASIC STRUCTURE OF IMMUNOGLOBULINS:

The basic structure of the immunoglobulins is illustrated in figure 2. Although different immunoglobulins can differ structurally, they all are built from the same basic units.

A. Heavy and Light Chains:

All immunoglobulins have a four-chain structure as their basic unit. They are composed of two identical light chains (23kD) and two identical heavy chains (50-70kD).

B. Disulfide bonds:

1. **Inter-chain disulfide bonds** - The heavy and light chains and the two heavy chains are held together by inter-chain disulfide bonds and by non-covalent interactions The number of inter-chain disulfide bonds varies among different immunoglobulin molecules.

2. **Intra-chain disulfide binds** - Within each of the polypeptide chains there are also intra-chain disulfide bonds.

C. Variable (V) and Constant (C) Regions

A. Fab:

Digestion with papain breaks the immunoglobulin molecule in the hinge region before the H-H inter-chain disulfide bond Figure 4. This results in the formation of two identical fragments that contain the light chain and the VH and CH1 domains of the heavy chain.

Antigen binding - These fragments were called the Fab fragments because they contained the antigen binding sites of the antibody. Each Fab fragment is monovalent whereas the original molecule was divalent.

B. Fc:

Digestion with papain also produces a fragment that contains the remainder of the two heavy chains each containing a CH2 and CH3 domain. This fragment was called Fc because it was easily crystallized.

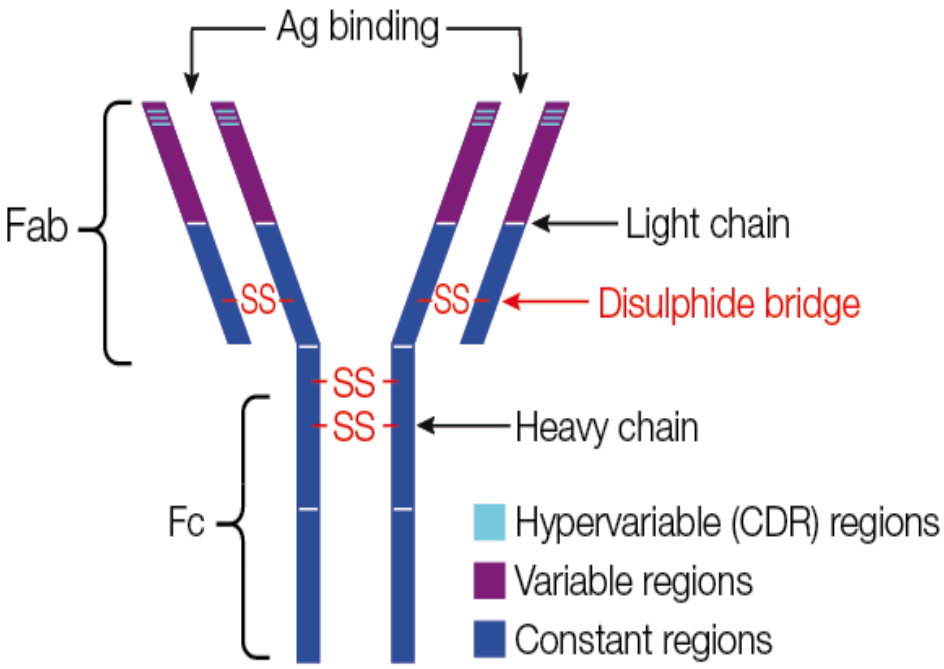

Figure 4 Structure of Immunoglobulin

HUMAN IMMUNOGLOBULIN CLASSES, SUBCLASSES

A. Immunoglobulin classes

The immunoglobulins can be divided into five different classes, based on differences in the amino acid sequences in the constant region of the heavy chains. All immunoglobulins within a given class will have very similar heavy chain constant regions. These differences can be detected by sequence studies or more commonly by serological means (i.e. by the use of antibodies directed to these differences) .

1. IgG - Gamma heavy chains

2. IgM - Mu heavy chains

3. IgA - Alpha heavy chains

4. IgD - Delta heavy chains

5. IgE - Epsilon heavy chains

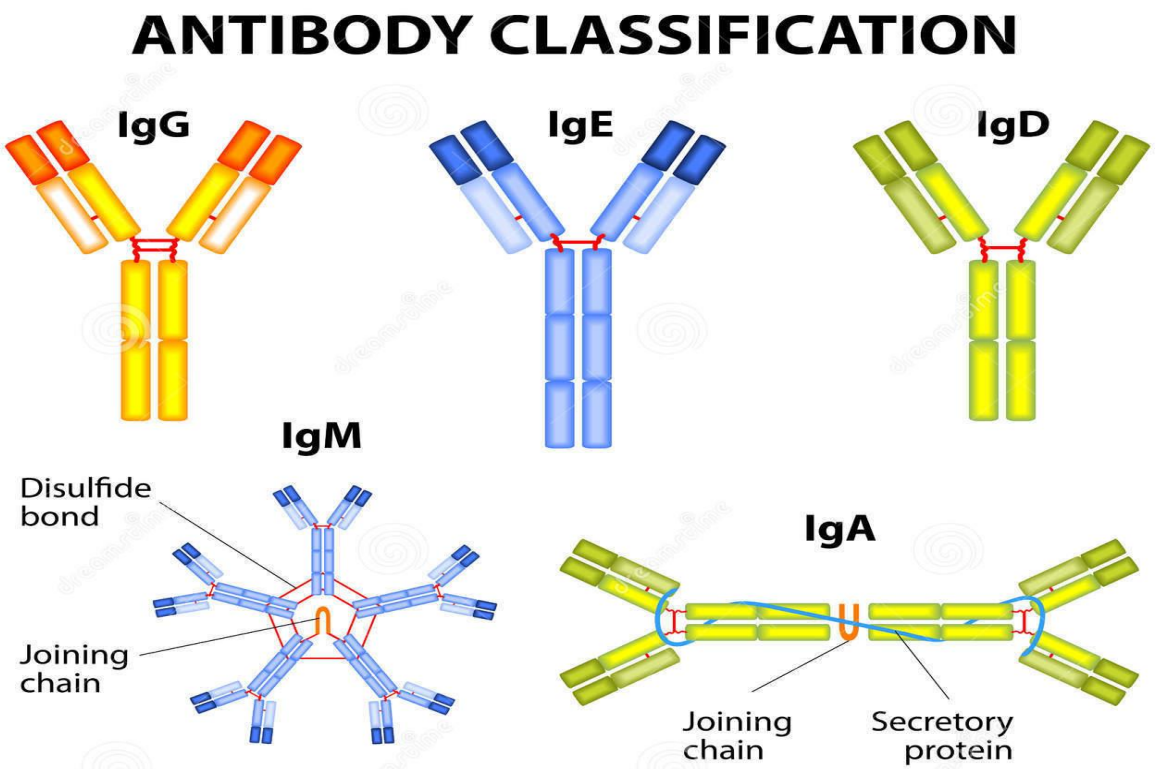

Figure 5 Classification of Antibody

Intravenous Immunoglobulin:

Intravenous immunoglobulin (IVIG) is a safe preparation made from sterilized purified human plasma from thousands of healthy donors per batch. Therefore, IVIG most likely contains the entire wide spectrum of variable regions present in normal plasma.1–3 IVIG contains more than 95% intact immunoglobulin G (IgG) molecules, with traces of immunoglobulin A (IgA) (<2.5%) and immunoglobulin M (IgM) (negligible). The IgG subclasses distribution corresponds to that of normal human plasma. 1–4 Petaglobin, an IVIG preparation, is IgM enriched .

The therapeutic immunomodulatory effect of IVIG lies within its content. A standard IVIG preparation contains natural antibodies that are more polyreactive than are immune antibodies, including IgG antibodies against endogenous antibodies. These IgG antibodies are known to be anti-idiotypic and are able to neutralize and immunomodulate autoantibodies.3,4 IVIG also contains natural autoantibodies against DNA, phospholipids, gangliosides, and glycolipid-sulfatide,6,7 as well as IgG antibodies against exogenous antigens (bacteria, viruses, etc.),

F(ab′)2 fragments of IgG, immunomodulating peptides (CD4, CD8, CD95, etc.), and various cytokines (interleukin [IL]–2, IL-4, IL-10, transforming growth factor β, etc.) .

Importantly, the natural autoantibodies (i.e., antiphospholipid and anti-DNA autoantibodies) within IVIG are nonpathogenic *in vivo,* most likely because of low affinity toward the autoantigenic target.IVIG, when administered properly to a selected patient population, was shown to be an effective treatment in autoimmune and cancer diseases, as well as for recurrent pregnancy loss, with side effects that are mostly mild and transient .

THE HISTORY OF IVIG:

The origin of IVIG use dates back to 1930 at Boston City Hospital, where a clinical experiment was conducted from 1919 to 1929 by M. Finland, in which equine serum was given to treat pneumococcal pneumonia. Although the treatment had side effects, namely, acute febrile reactions and serum sickness, it seemed that the therapy improved survival from pneumonia.13 In 1940, Edwin J. Cohn from Harvard University used human albumin from 19 donors to treat combat shock in soldiers wounded on the battlefield in World War II. In 1941, Cohn developed a process to produce human albumin (using ethanol as a precipitant) and recognized fractions containing gamma globulin, as well as prothrombin, lipoproteins, and other proteins .

Cohn acknowledged the importance of the globulins as a potent substitute "for convalescent serum." Cohn's collaborator, Oncley, separated (by molecular weight) the gamma globulins from prothrombin, plasminogen, and isohemagglutinins.15 After World War II, in the mid-1940s, injections of separated gamma globu**SAPIR *et al.*: INTRAVENOUS IMMUNOGLOBULINS 745** lins became common as a substitute for earlier placental extract preparations of globulin, mainly to prevent or attenuate viral diseases .

The first use of gamma globulin that was not related to infections or immunodeficiencies was attempted in the 1940s by Diamond, who worked with Cohn's fractions and tried to develop an anti-Rh globulin to prevent erythroblastosis fetalis.14 However, the use of intravenous administration of gamma globulins was discontinued after Janeway17 found it to be the frequent cause of immediate vasomotor reactions, chills, and fever .

Imbach was the first to observe that the IVIG treatment improved the condition of the children with immunodeficiency and ameliorated the thrombocytopenia. Imbach immediately

implemented this treatment for idiopathic thrombocytopenia purpura (ITP), indicating the efficacy of IVIG in other autoimmune conditions .

IVIG has been given for a variety of autoimmune, inflammatory, and neurologic diseases and many other conditions. In some diseases, a beneficial effect was proved, such as in ITP and Kawasaki syndrome, whereas in others it is still debatable, for example, multiple sclerosis .

Usage of IVIG in Disease:

"Multiple Ailments
One Treatment"

IVIG has many uses and is an important treatment in many diseases. The original use was as replacement therapy (400-600 mg/kg/month) in primary and secondary antibody deficiencies. However, IVIG has many immunomodulatory and anti-inflammatory effects at higher doses (2 g/kg/d) and now more than 100 inflammatory and autoimmune disorders are treated with IVIG .

Several IVIG preparations are available and are supplied in either a lyophilised form or as ready-to-use solutions. IVIG therapy has a few proven indications and many potential ones. There are currently six clinical indications in the USA with Food and Drug Administration (FDA) approval

- ✓ Treatment of primary immunodeficiencies.
- ✓ Prevention of bacterial infections in patients with hypogammaglobulinaemia and recurrent infection caused by B-cell chronic lymphocytic leukaemia.
- ✓ Prevention of coronary artery aneurysms in
- ✓ Kawasaki disease.
- ✓ Prevention of infections, pneumonia and acute graftversus-host disease (GVHD) after bone marrow transplantation.

- ✓ Reduction of serious bacterial infection in children with HIV.
- ✓ Increase of platelet count in idiopathic thrombocytopenic purpura to prevent or control bleeding.

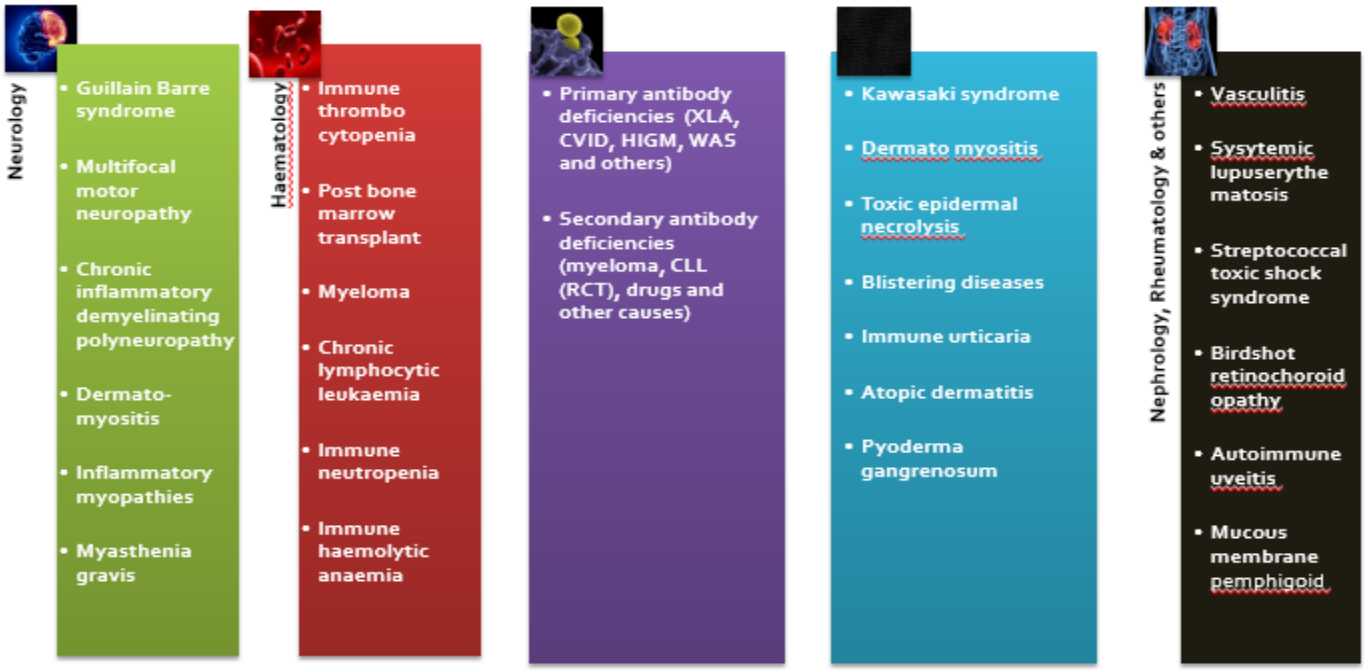

Figure 6: Uses of IVIG

Primary and secondary immunodeficiency:

Primary immunodeficiency diseases (PI) are a group of more than 350 rare, chronic disorders in which part of the body's immune system is missing or functions improperly. While not contagious, these diseases are caused by hereditary or genetic defects, and, although some disorders present at birth or in early childhood, the disorders can affect anyone, regardless of age or gender .

Some affect a single part of the immune system; others may affect one or more components of the system. And while the diseases may differ, they all share one common feature: each result from a defect in one of the functions of the body's normal immune system .

In the most common PIDDs, different forms of these cells or proteins are missing or do not function. This creates a pattern of repeated infections, severe infections and/or infections that are unusually hard to cure. These infections may attack the skin, respiratory system, the ears, the brain or spinal cord, or in the urinary or gastrointestinal tracts.

Sign & Symptoms:

• Recurrent, unusual or difficult to treat infections

• Poor growth or loss of weight

• Recurrent pneumonia, ear infections or sinusitis

• Multiple courses of antibiotics or IV antibiotics necessary to clear infections

• Recurrent deep abscesses of the organs or skin

• A family history of PID

• Swollen lymph glands or an enlarged spleen

Primary Immunodeficiency Disease Treatment & Management:

1. bone marrow transplantation
2. stem cell transplantation
3. IVIG

The use of IVIG in primary and secondary antibody deficiencies has been thoroughly reviewed by Stiehm. Patients with primary antibody deficiencies are susceptible to bacterial infections and require lifelong immunoglobulin replacement therapy. In primary or secondary hypogammaglobulinemia IVIG protects against infection by providing an adequate concentration of IgG .

Dosage of IVIG in primary antibody deficiencies

The usual dose of IVIG for antibody replacement is between **400-600 mg/kg every 2-4 weeks.** The dose is adjusted so that the trough level just before the next infusion is at least 500 mg/dl. For other uses the doses range between 400 mg/kg/day for 5 days or a more rapid course of 1-2 g/kg given over 1-2 days .

Immune Thrombocytopenic Purpura

Idiopathic thrombocytopenic purpura (ITP) is a disorder that can lead to easy or excessive bruising and bleeding. The bleeding results from unusually low levels of platelets — the cells that help blood clot .

Idiopathic thrombocytopenic purpura, which is also called immune thrombocytopenia, affects children and adults. Children often develop ITP after a viral infection and usually recover fully without treatment. In adults, the disorder is often long term.

If you don't have signs of bleeding and your platelet count isn't too low, you may not need any treatment. In rare cases, the number of platelets may be so low that dangerous internal bleeding occurs .

Symptoms

Idiopathic thrombocytopenic purpura (ITP) may have no signs and symptoms. When they do occur, they may include:

- Easy or excessive bruising (purpura)
- Superficial bleeding into the skin that appears as a rash of pinpoint-sized reddish-purple spots (petechiae), usually on the lower legs
- Bleeding from the gums or nose
- Blood in urine or stools
- Unusually heavy menstrual flow

Treatment

- ✓ Oral corticosteroids
- ✓ IV immune globulin (IVIG)
- ✓ IV anti-D immune globulin
- ✓ Splenectomy
- ✓ Rituximab

Dosage of IVIG in ITP:

The effectiveness of IVIG in increasing platelet counts has been supported in numerous studies, resulting in an FDA-approved indication of its use. Importantly, high-dose IVIG has been compared to systemic corticosteroids in randomized, multicenter trials, and was found to

provide a clinically relevant advantage Thus, at present, IVIG remains an important and useful treatment modality for preventing or controlling bleeding in the more severe presentations of immune-mediated thrombocytopenia. Dosage of IVIG in ITP is 1gm/kg for 5 days .

Guillain-Barré syndrome

Guillain-Barré syndrome is a rare but serious autoimmune disorder in which the immune system attacks healthy nerve cells in your peripheral nervous system. This leads to weakness, numbness, and tingling. It can eventually cause paralysis. The cause of this condition is unknown, but it's typically triggered by an infectious illness, such as the stomach flu or a lung infection .

Guillain-Barré is rare, affecting only about 1 in 100,000 Americans, according to the National Institute of Neurological Disorders and Stroke. There's no cure for the syndrome, but treatment can reduce the severity of your symptoms and shorten the duration of the illness .

There are multiple types of Guillain-Barré, but the most common form is acute inflammatory demyelinating polyradiculoneuropathy (AIDP). It results in damage to myelin. Other types include Miller Fisher syndrome, which affects the cranial nerves.

The symptoms of Guillain-Barré include:

- ✓ tingling or prickly sensations in your fingers and toes
- ✓ muscle weakness in your legs that travels to your upper body and gets worse over time
- ✓ difficulty walking steadily
- ✓ difficulty moving your eyes or face, talking, chewing, or swallowing
- ✓ severe lower back pain
- ✓ loss of bladder control
- ✓ fast heart rate
- ✓ difficulty breathing
- ✓ paralysis

TREATMENT:

1. Intravenous immunoglobulin
2. Plasmapheresis (plasma exchange)

Dosage: The usual dose of IVIG for Guillain-Barré syndrome is 2g/kg.

Kawasaki disease

Kawasaki disease (KD) is an acute, self-limited febrile illness of unknown cause that predominantly affects children <5 years of age. When initially described, the potential for coronary artery complications was not appreciated. KD is now the most common cause of acquired heart disease in children in developed countries .

In the absence of pathognomonic tests, the diagnosis continues to rest on the identification of principal clinical findings and the exclusion of other clinically similar entities with known causes. Timely initiation of treatment with intravenous immunoglobulin (IVIG) has reduced the incidence of coronary artery aneurysms defined from absolute luminal dimensions from 25% to ≈4%.

Ongoing studies with additional therapies have not substantially reduced this residual risk. The long-term prognosis is determined by the initial and current level of coronary artery involvement. Certain subsets of patients are at risk for myocardial ischemia from coronary artery thrombosis and stenoses. Medical management of such patients hinges on judicious use of thromboprophylaxis and vigilance to identify evolving stenoses. Invasive revascularization procedures might be required for selected patients .

Signs and symptoms

Kawasaki disease produces prolonged fever (often abrupt in onset and preceded by several days of nonspecific symptoms) along with a constellation of clinical features that includes the following :

- ✓ Irritability
- ✓ Nonexudative bilateral conjunctivitis (90%)
- ✓ Anterior uveitis (70%)
- ✓ Perianal erythema (70%)
- ✓ Sterile pyuria
- ✓ Erythema and edema on the hands and feet; the latter impedes ambulation

- ✓ Strawberry tongue and lip fissures
- ✓ Hepatic, renal, and GI dysfunction
- ✓ Myocarditis and pericarditis
- ✓

Dosage:

IVIG relieves acute inflammation and has been shown to reduce the rate of coronary aneurysms from greater than 25% in untreated patients to 1-5% in treated patients. Maximal benefits are seen when IVIG is given within the first 10 days of the illness. In current practice, the dose is 2 g/kg intravenously over 10-12 hours .

Chronic inflammatory demyelinating polyneuropathy (CIDP)

Chronic inflammatory demyelinating polyneuropathy (CIDP) is a neurological disorder characterized by progressive weakness and impaired sensory function in the legs and arms. The disorder, which is sometimes called chronic relapsing polyneuropathy, is caused by damage to the myelin sheath (the fatty covering that wraps around and protects nerve fibers) of the peripheral nerves .

Although it can occur at any age and in both genders, CIDP is more common in young adults, and in men more so than women. It often presents with symptoms that include tingling or numbness (beginning in the toes and fingers), weakness of the arms and legs, loss of deep tendon reflexes (areflexia), fatigue, and abnormal sensations. CIDP is closely related to Guillain-Barre syndrome and it is considered the chronic counterpart of that acute disease .

Signs and symptoms

CIDP typically starts insidiously and evolves slowly, in either a slowly progressive or a relapsing manner, with partial or complete recovery between recurrences; periods of worsening and improvement usually last weeks or months. Most experts consider the necessary duration of symptoms to be greater than 8 weeks for the diagnosis of CIDP to be made .

Symptoms reported include the following:

- ✓ Preceding infection (infrequent)

- ✓ Initial limb weakness, both proximal and distal
- ✓ Sensory symptoms (eg, tingling and numbness of hands and feet)
- ✓ Motor symptoms (usually predominant)
- ✓ In about 16% of patients, a relatively acute or subacute onset of symptoms
- ✓ In children, usually a more precipitous onset of symptoms
- ✓ Symptoms of autonomic system dysfunction (eg, orthostatic dizziness)

Treatment:

1. **Glucocorticoid:**

Glucocorticoid drugs such as prednisone have proven effective in treating individuals with CIDP. In many cases, individuals with CIDP may respond to corticosteroid treatment alone. However, individuals requiring high doses of corticosteroid drugs may experience side effects that deter long-term therapy .

2. **Intravenous immunoglobulin:**

Intravenous immunoglobulin (IVIG) has been proven to be effective and is often used as a treatment for chronic inflammatory demyelinating polyneuropathy. IVIG can enhance the immune system. Very high doses are usually used for initial treatment of CIDP and most patients require continued intermittent treatments. There is a clinical trial of a subcutaneous delivery of immunoglobulin that may be used instead of IVIG .

3. **Plasma exchange**

Plasma exchange (PE) has also been shown to be of benefit in chronic inflammatory demyelinating polyneuropathy. This procedure is a method for removing unwanted substances (toxins, metabolic substances and plasma parts) from the blood. Blood is removed from an affected individual and blood cells are separated from plasma. The plasma is then replaced with other human plasma and the patient's blood cells are transfused back into the affected individual, thus removing only the plasma and its constituents. Similar to IVIG, PE is effective only for a few weeks and may require chronic intermittent treatments .

Dosage:

The usual initiating dose of intravenous immunoglobulins (IVIg) in the treatment of chronic inflammatory demyelinating polyneuropathy (CIDP) is 0.4g/kg/day for 5 days.

Multifocal motor neuropathy

Multifocal motor neuropathy (MMN) is a rare neuropathy characterized by progressive, asymmetric muscle weakness and atrophy (wasting). Signs and symptoms include weakness in the hands and lower arms; cramping; involuntary contractions or twitching; and atrophy of affected muscles. MMN is thought to be due to an abnormal immune response, but the underlying cause is not clear. Most people treated with intravenous immune globulin (IVIG) have rapid improvement in weakness, but maintenance IVIG is usually required for sustained improvement .

Pathophysiology

The complete cascade of events leading to motor nerve dysfunction and weakness in MMN is not fully understood, but it appears to be related to dysimmune events. Histopathologic and electrodiagnostic studies demonstrate the presence of both demyelinating and axonal injury .

Motor nerves are primarily affected, although mild demyelination has been demonstrated in sensory nerves as well. Efficacy of immunomodulatory and immunosuppressive treatment further supports the immune nature of MMN. Rare cases of MMN have been reported following treatment with tumor necrosis factor (TNF)-α antagonists .

Signs and symptoms

- ✓ Weakness
- ✓ Cramping
- ✓ involuntary contractions
- ✓ twitching
- ✓ wasting (atrophy) of affected muscles.

Treatment

Multifocal motor neuropathy (MMN) is considered treatable with **intravenous immune globulin (IVIG).** Early treatment shortly after symptoms begin is recommended. Most people have a fairly rapid improvement in weakness with IVIG, but the improvement generally does

not last beyond a few months. Maintenance IVIG infusions are usually needed every two to six weeks. For those with severe disease whose symptoms don't respond to IVIG (or for those who become resistant), treatment options are limited. Several reports have suggested that cyclophosphamide may be partially effective

Autoimmune hemolytic anemia

Idiopathic autoimmune hemolytic anemia is a form of autoimmune hemolytic anemia. Autoimmune hemolytic anemia (AIHA) is a group of rare but serious blood disorders. They occur when the body destroys red blood cells more rapidly than it produces them. A condition is considered idiopathic when its cause is unknown .

Autoimmune diseases attack the body itself. Your immune system produces antibodies to help target foreign invaders such as bacteria and viruses. In the case of autoimmune disorders, your body mistakenly produces antibodies that attack the body itself. In AIHA, your body develops antibodies that destroy red blood cells .

Idiopathic AIHA can be life-threatening because of its sudden onset. It requires immediate medical attention and hospitalization.

Symptoms of idiopathic AIHA

You may feel weak and short of breath if you develop sudden-onset idiopathic AIHA. In other instances, the condition is chronic and develops over time, so symptoms are less obvious. In both cases, symptoms may include one or more of the following:

- ✓ increasing weakness
- ✓ shortness of breath
- ✓ rapid heartbeat
- ✓ pale or yellow-colored skin
- ✓ muscle pain
- ✓ nausea
- ✓ vomiting
- ✓ dark-colored urine
- ✓ a headache
- ✓ abdominal discomfort
- ✓ bloating

- ✓ diarrhea

Treatment options for AIHA

1. Steroids

The first-line treatment is typically steroids such as prednisone. They may help improve red blood cell counts. Your doctor will carefully monitor you to check that the steroids are working. Once your condition goes into remission, your doctor will try to wean you off of the steroids slowly. People with AIHA undergoing steroid therapy may need supplements during treatment. These could include :

- bisphosphonates
- vitamin D
- calcium
- folic acid

2. Surgery

Your doctor may suggest surgical removal of the spleen if the steroids don't work completely. Removal of the spleen can reverse the destruction of red blood cells. This surgery is known as a splenectomy. Two-thirds of people who undergo a splenectomy have a partial or total remission from their AIHA, and people with the idiopathic type tend to have the most successful results .

3. Immune-suppressing drugs

Other treatment options are immune-suppressing drugs, such as azathioprine and cyclophosphamide. These can be effective medications for people who don't successfully respond to treatment with steroids or who aren't candidates for surgery .

Chronic lymphocytic leukemia

Chronic lymphocytic leukemia (CLL) is a type of cancer of the blood and bone marrow — the spongy tissue inside bones where blood cells are made.

The term "chronic" in chronic lymphocytic leukemia comes from the fact that it typically progresses more slowly than other types of leukemia. The term "lymphocytic" in chronic lymphocytic leukemia comes from the cells affected by the disease — a group of white blood cells called lymphocytes, which help your body fight infection .

Chronic lymphocytic leukemia most commonly affects older adults. There are treatments to help control the disease.

Symptoms

Many people with chronic lymphocytic leukemia have no early symptoms. Those who do develop signs and symptoms may experience:

- Enlarged, but painless, lymph nodes
- Fatigue
- Fever
- Pain in the upper left portion of the abdomen, which may be caused by an enlarged spleen
- Night sweats
- Weight loss
- Frequent infections

Treatments

1. **Chemotherapy:** Chemotherapy is a drug treatment that kills quickly growing cells, including cancer cells. Chemotherapy treatments can be administered through a vein or taken in pill form. Depending on your situation, your doctor may use a single chemotherapy drug or you may receive a combination of drugs .
2. **Targeted drug therapy**: Targeted drugs are designed to take advantage of the specific vulnerabilities of your cancer cells. Your cancer cells are tested to determine which targeted drugs may be helpful .
3. **Immunotherapy:** Immunotherapy is a treatment that uses your body's immune system to fight cancer. Immunotherapy treatments may make it easier for your immune system to identify cancer cells or train your immune system cells to fight cancer cells .

4. **Bone marrow transplant:** A bone marrow transplant, also known as a stem cell transplant, uses strong chemotherapy drugs to kill the stem cells in your bone marrow that are creating diseased lymphocytes. Then healthy adult blood stem cells from a donor are infused into your blood, where they travel to your bone marrow and begin making healthy blood cells .
5. **Intravenous Immunoglobulin:** The usual initiating dose of intravenous immunoglobulins (IVIg) in the treatment of CLL is 0.4g/kg to maintain 4 - 6 gm/l IgG level in Blood

Research Methodology

- ✓ Study Type: Descriptive study
- ✓ Study Duration: Three Months (5thFebruary to 4th May)

- ✓ Tool used: MS-Excel 2016
- ✓ Data Collection method: The secondary data was used. Secondary data for competitor analysis and market trends.
- ✓ Source of Secondary data:

Secondary Research we refer a broad array of industry sources for our secondary research, which typically include; however, not limited to:

- o Company annual reports, company websites, & financial reports and investor presentations for competitive scenario and shape of the industry
- o Scientific and technical writings for product information and related preemptions
- o Authentic new articles, web-casts and other related releases for market evaluation
- o 〕Internal and external proprietary databases, key market indicators and relevant press releases for market estimates and forecast

Objectives:

- ✓ To understand the wide usage of IVIG in different indications.
- ✓ To understand the global market of IVIG.
- ✓ To determine the market share of different brands of medicine Available in market.
- ✓ To understand the global market trends of IVIG

MARKET OVERVIEW OF IVIG

Global Market Overview

The global market for intravenous immunoglobulin (IVIG) products and therapies is heading in a positive direction due to several innovative techniques and advantages it offers to clinicians worldwide. The market is expected to expand at a healthy pace in the near future. Factors that

will support market's growth include technological improvements in the methods used for production and purification of IVIG products and an improving health care infrastructure across the globe .

The rising patient pool suffering from immunological and neurological disorders, mounting geriatric population, and rising production of IVIG products are also expected to have a significant positive impact on market's future growth prospects .

The world IVIG market was evaluated at **$7,861.5 million** in 2015, and is projected to reach **$12,632.5 million** by 2022, with a CAGR of 7.1% during the forecast period .

Figure 7 : Global Market Growth of IVIG

It is growing at a rapid pace due to the increase in prevalence of chronic inflammatory demyelinating polyneuropathy (CIDP) and hypogammaglobinemia and rise in use of immunoglobulins to treat Guillain–Barré syndrome (GBS), inflammatory myopathies, specific antibody deficiency, and others. In addition, rise in number of approvals for IVIG products from Food and Drug Administration (FDA), European Medicine Agency (EMA), and government help to accelerate the immunoglobulin industry .

The increase in geriatric population and number of hemophilic patients, improved IVIG production owing to the emergence of advanced technologies, and enhanced purification techniques (with better plasma yield) drives the market. However, stringent government

regulations, expensive therapy, and high risk of side effects associated with the use of IVIG are expected to hamper the market growth .

MARKET DEFINITION AND SCOPE

IVIG are antibodies that are used in the treatment of patients suffering from antibody deficiencies. Currently, IVIG is used for several FDA and European Medical Agency (EMA) approved indications and several off-label indications, therefore, the report covers the revenue generated from all these indications .

Application segment includes Hypogammaglobulinemia, immunodeficiency, CIDP, Myasthenia Gravis (MG), Multifocal motor neuropathy (MMN), ITP, Inflammatory myopathies, Specific antibody deficiency (SAD), GBS, and others. Other application covers specific antibody deficiency, Inflammatory Myopathies, and other off-label indications .

The application market segment is deduced with the help of IVIG adoption pattern for each indication in different economies along with the incidence and prevalence rate of these indications .

GLOBAL IVIG MARKET, BY GEOGRAPHY

Geographically, the IVIG market segments across four geographies namely, North America, Europe, Asia-Pacific, and LAMEA (Latin America, Middle East, and Africa).

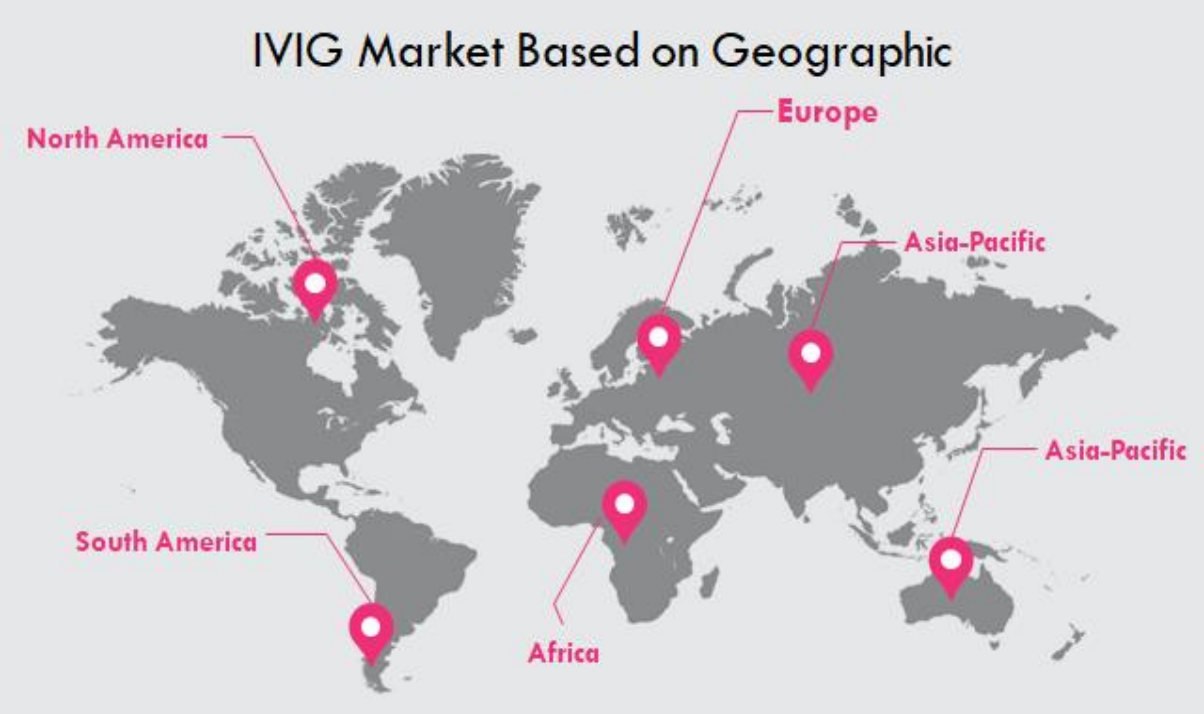

Figure 8:Global IVIG Market by Geographic

Various regulatory authorities such as USFDA, EMA, the Japanese Pharmaceuticals and Medical Devices Agency, the Australian Therapeutic Goods Administration, and Health Canada, regulate the manufacture, distribution, and sale of IVIG in their respective regions .

North America leads the IVIG market as majority of the multinational players belong to this region. North America is projected to dominate the IVIG market, followed by Asia-Pacific due to high adoption of its treatments, high plasma collection, and large patient population .

LAMEA is expected to grow at a high CAGR of 10% growing to the increase in preference of IVIG therapies and growth in awareness about immunodeficiency diseases in the underdeveloped regions. The global IVIG market, by geography, is expected to grow from **$7,861.5 million** in 2015 to **$12,632.5 million** by 2022, at an estimated CAGR of 7.1% from 2016 to 2022 .

MARKET SIZE AND FORECAST

The North American region PID market valued at $1678 million in 2015 and is estimated to reach $2261 million by 2022 growing at a CAGR 6.1% during the forecast period 2016-2022, The EUROPE IVIG market was valued at $2150 million in 2015 and is expected to reach $3000 million, growing at a CAGR of 6 % during the 2015 – 2022 ..

NORTH AMERICA

North America PID market is further segmented across United States, Canada, and Mexico. The North America PID market was valued at $1678 million in 2015 and is expected to reach $2661 million, growing at a CAGR of 6.1% during the analysis period .

The U.S. National library of Medicine and the National Institute of Health published a report, in 2012, about 6 million patients suffered from PID (Primary immunodeficiency Diseases) globally and is expected to grow further, representing the potential growth for the treatment of hypogammaglobulinemia in the coming years

North America held the largest regional market share in terms of revenue in 2014 due to the presence of:

- ✓ a well-regulated healthcare system
- ✓ the larger pool of target population
- ✓ high patient awareness pertinent to the plasma protein product.

China Market

Figure 9:IVIG sales in China

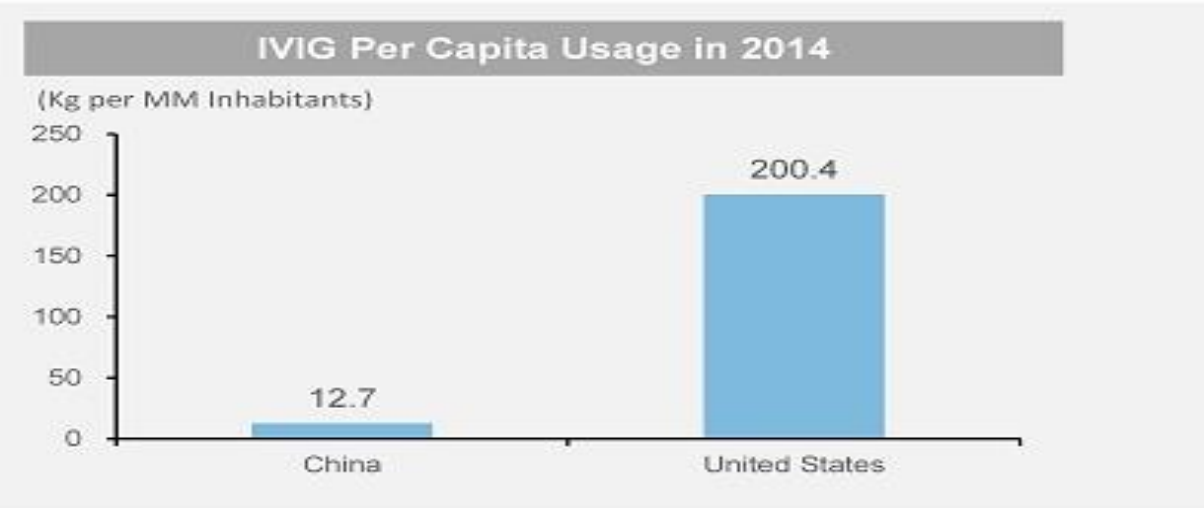

Figure 10 : IVIG per capita Usage in 2004

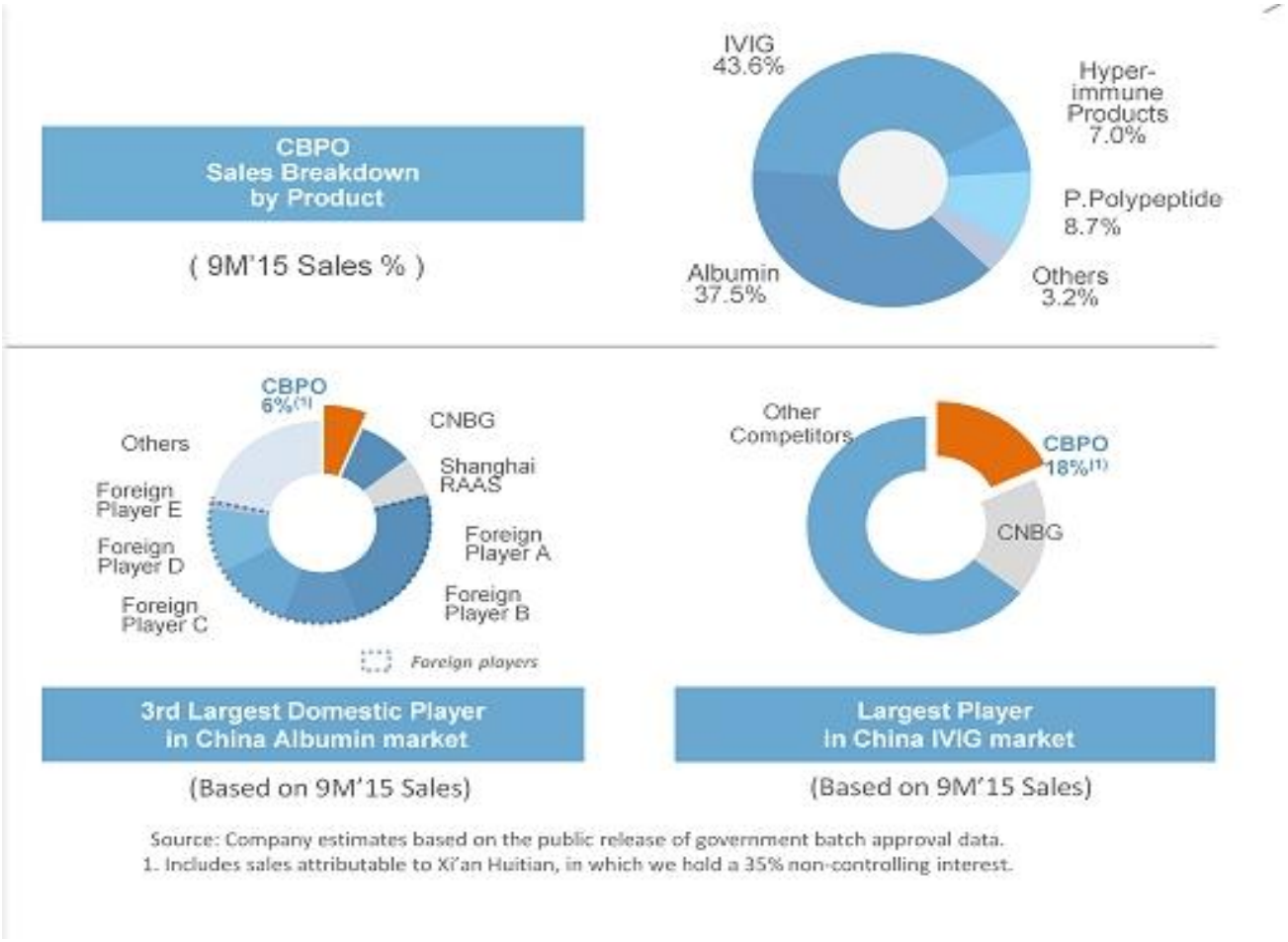

Figure 11: Plasma product market in China

EUROPE

The EUROPE IVIG market was valued at $2150 million in 2015 and is expected to reach $3000 million, growing at a CAGR of 6 % during the 2015 – 2022.

In EUROPE, the French IVIG market was valued at $299 million in 2015, and is expected to reach $474 million by 2022, with a CAGR of 6%

Globally Key players operating in the IVIG market:

1. Baxter international Inc.

2. CSL Limited
3. Grifols S.A
4. Octapharma Ag
5. Kedrion Pharma
6. LFB group
7. Biotest AG
8. China Biologics Products, Inc.
9. BDI Pharma
10. Bayer Healthcare.

Market Share of global company:

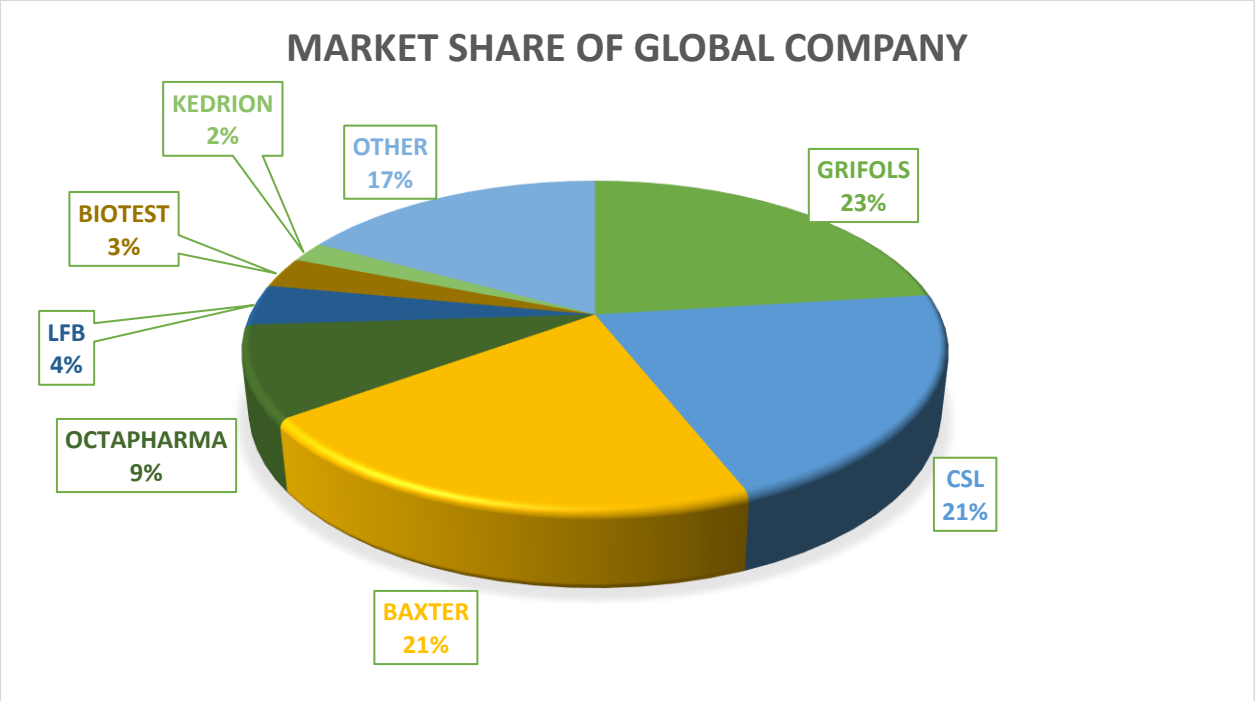

Figure 12: IVIG Market share of Global Companies

Product available in Global Market:

S./no	COMPANY	BRAND NAME	CONCENTRAT-IONS	SIZES
1.	CSL Behring	Carimune NF	3%,6%, 9%, 12%	3g, 6g, 12g
2.	Grifols	Flebogamma 5% DIF	5%	2.5g, 5g, 10g, 20g
3.	Grifols	Flebogamma 10% DIF	10%	5g, 10g, 20g
4.	Shire	Gammagard	5%, 10%	5g, 10g
5.	Bio Product Lab.	Gammaplex 5%	5%	5g, 10g, 20g
6.	Bio Product Lab.	Gammaplex 10%	10%	5g, 10g, 20g
7.	Octapharma	Octagam 5%	5%	1g, 2.5g, 5g, 10g, 25g
8.	Octapharma	Octagam 10%	10%	2g, 5g, 10g, 20g
9.	CSL Behring	Privigen	10%	5g, 10g, 20g, 40g

Table 2 : IVIG product available in global market

INDIA Market Overview:

India is the seventh largest country in terms of area and the second most populous country in the world. It has a plethora of natural resources and assets like the rich agricultural lands, deep gold and gemstone mines, some of the largest rivers, and, most importantly, its 1.2 billion people, which hold huge potential in more ways than one1 .

Plasma is one such resource, which India could have in abundance, but its potential is still unrealized. Being the youngest and second most populous country, India has a huge blood/plasma donor base which can greatly contribute to the local, as well as, global plasma product industry. Unfortunately for a variety of reasons, this potential is not explored and tapped to its fullest. The challenges in the Indian plasma industry are intense and prevalent at all the stages right from the start until the end point. India collects about 10 million of blood at more than 2700 blood banks across the country. These blood banks are in public, private, charitable, and hospital settings. As per the Drug and Cosmetic Act, each unit of blood is tested for HIV-I and HIV-II antibodies, Malaria, Syphilis, Hepatitis B surface antigen and Hepatitis C virus antibody and componentized within 6 hours of collection

Indian Scenario

India needs about 900,000 liters of plasma proteins per year. The overall demand of various plasma derived products are depicted in the table 3 Import of size of these products in year 2014-15 and their cost.

Table 3: overall current demand of albumin , coagulation factor VIII and IX , and intravenous immunoglobulin

Albumin	**IVIG**	Factor VIII	Factor IX
8-10 lac vials	**3 -4 lac vials**	80-100 million IUs	10-15 Million IUs
20 gm/ 100 ml	**5 gm/100 ml**	250 IUs	500 IUs

Table 3 : Current Demand of IVIG

Size of indigenously manufactured these products in year 2014-15.			
1	albumin :	: 3 lac vials	With NPPA rate : Rs. 4038 per vial : Rs. 120 Cr.
2	**IVIG**	**60000 vials**	at the rate : Rs. 7500/vial : Rs. 45 Cr
3	Factor VIII	It is largely imported at the rate of Rs. 13-22 IUs	

Table 4 :No. of Vials Manufactured

The Indian market for intravenous immunoglobulin (IVIG) products and therapies is heading in a positive direction due to several innovative techniques and advantages it offers to clinicians worldwide .

The market is expected to expand at a healthy pace in the near future. Factors that will support market's growth include technological improvements in the methods used for production and purification of IVIG products and an improving health care infrastructure across the globe. The rising patient pool suffering from immunological and neurological disorders, mounting geriatric population, and rising production of IVIG products are also expected to have a significant positive impact on market's future growth prospects .

The Indian intravenous immunoglobulin (IVIG) market is largely consolidated, with top four players:

1. Reliance Life Sciences
2. Intas Pharmaceuticals Ltd.
3. PlasmaGen BioSciences
4. Wockhardt Limited

Company Landscape of IVIg:

Company	Brand name	Strength	MRP	Market share in unit(Per Month)	Market share in Crore
Reliance	Immunorel	5%,	₹16500	5250	7.71
Intas	Globucel	5%,	₹13507	3245	4.79
PlasmaGen	PlasmaGlob	5%,	₹14697	1700	2.49
Wockhardt	Globuwok	5%,	₹17061	1365	2.00
Bharat Serum	Gamma IV	5%,	₹17036	720	1.05
Biocon	Ivnex	5%,	₹7334	345	0.50
Emcure	Emglobulin	5%	₹13190	90	.013
GSK	Seroglobulin	5%	₹15697	150	0.22
India buls	Immuglo	5%	₹14697	225	.33

Table 5 : IVIG product available in INDIA market

Market coverage

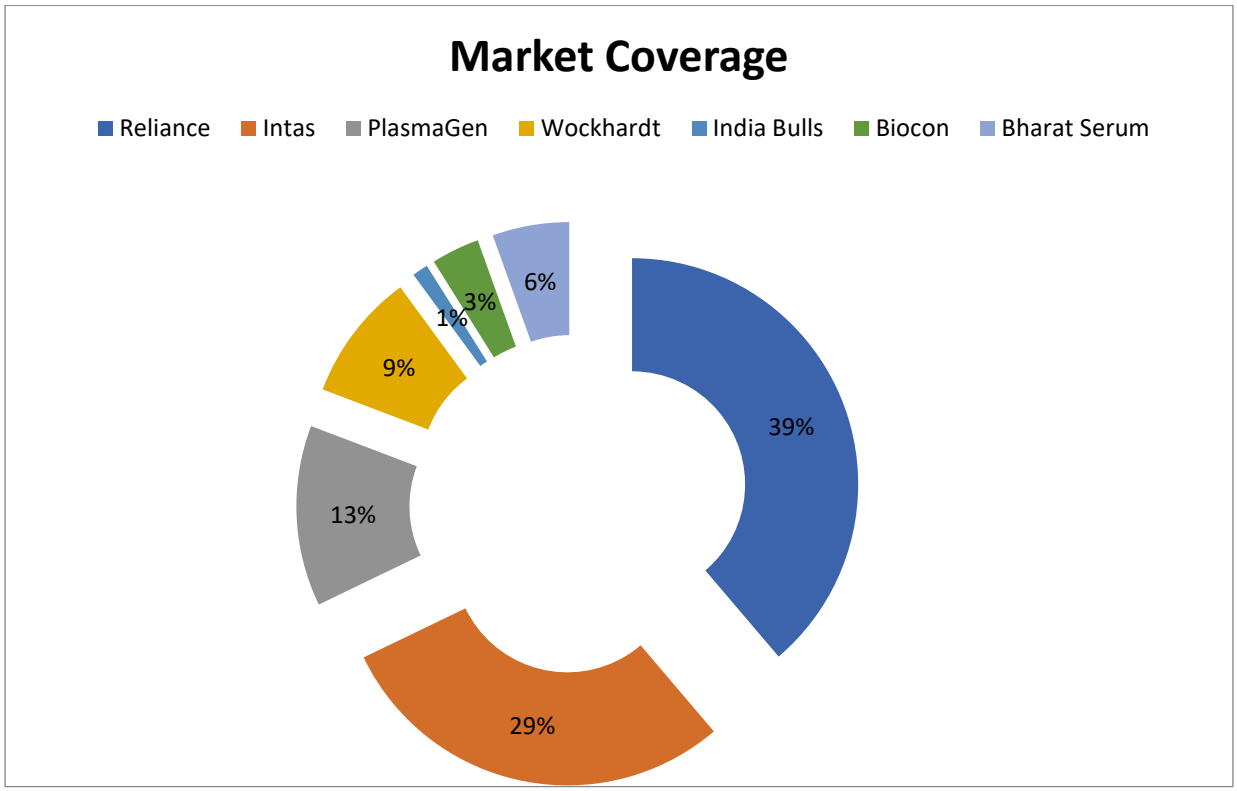

Figure 13 : Monthly Market coverage of indian companies in india

"An overview study of Intravenous

Immunoglobulin and global market scenario of IVIG"

By

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Dissertation submitted for the partial fulfillment of the

MBA Pharmaceutical Management

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Recommendations:

- Price is the important criteria for making brand successful, so price should be economical as well because many doctors rely on price factor because cost of IVIG therapy is very high especially in government hospital.
- According to the current market, the global IVIG market is segmented based on its application in the treatment of several conditions, i.e., CIDP, ITP, PID, Secondary Immunodeficiency in Chronic Lymphocytic Leukemia, Pediatric Human Immunodeficiency Virus (HIV) infection, Kawasaki disease, Specific antibody Deficiency, Acquired Hypogammaglobinemia, Myasthenia Gravis so we can easily segregate the market and segregate the potential customers like hematology, neurology, Rheumatology, Intensivist.
- The Neuro physician and Hemato oncologist re using IVIG in rare disorder so the companies should be actively promote their product to these doctors.
- Medical Literature should be provided to doctors to make them aware about the recent advance in plasma product and usage in newer indications.

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