



PRODUCT PROFILER

Immune Globulin
Subcutaneous (Human)

Vivaglobin[®]

For the Treatment of Primary Immunodeficiency
Diseases

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THE PRODUCT PROFILER

The Product Profiler provides P&T committee members with current, detailed information about a specific therapeutic agent to help them manage their formularies and establish medication-related policies. The Profiler provides information about pharmacology, clinical studies and FDA-approved indications, safety, efficacy, acquisition costs, and other pharmacoeconomic variables, along with additional P&T committee considerations, in a convenient package. Articles are written by experts in the field.

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DISCLOSURE

This work was funded by CSL Behring, maker of Vivaglobin®. The authors indicate that they have no direct relationship, financial or otherwise, with CSL Behring. For full information about Vivaglobin®, please refer to the prescribing information at the end of this profiler.



PRODUCT PROFILER

Immune Globulin Subcutaneous (Human)

Vivaglobin[®]

For the Treatment of Primary Immunodeficiency Diseases

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Immune Globulin Subcutaneous (Human)

Vivaglobin®

For the Treatment of Primary Immunodeficiency Diseases

INTRODUCTION

This Product Profiler introduces health care professionals to immune globulin subcutaneous (human), Vivaglobin®, a treatment for patients with primary immunodeficiency (PI) who require lifelong immunoglobulin (Ig) treatment. The term PI refers to a large, heterogeneous group of disorders that affect the cells, tissues, and proteins of the immune system. Vivaglobin is the first and only FDA-approved subcutaneous (SQ) immunoglobulin (SQIg) indicated for PI in the U.S. It can be self-administered by patients under a physician's care and after training from the physician or other health care provider.

Monthly intravenous immunoglobulin (IVIg) infusions are currently the standard therapy for PI in the U.S.; however, clinical studies have shown Vivaglobin to be a safe and effective alternative in the treatment of both adult and pediatric patients with PI. However, the safety and efficacy of this product have not been studied in pediatric subjects younger than two years of age.

When administered on a weekly basis, Vivaglobin provides stable steady-state serum immunoglobulin G (IgG) levels, with lower IgG peak levels and higher IgG trough levels compared with monthly IV treatment.

The following text presents a brief overview of PI and current treatment options, followed by a review of the evidence-based literature supporting the FDA-approved indications for the SQ administration of human normal Ig.

DISEASE BACKGROUND

Incidence and Prevalence

Primary immunodeficiency (PI) diseases comprise a diverse group of disorders in which the immune system fails to produce adequate amounts of antibodies, thereby predisposing individuals to increased risk of infection.¹ In contrast to secondary immune deficiency diseases, which are the result of external factors (e.g., viruses, drugs, antibiotics, and severe infections), PI diseases are caused by intrinsic or genetic defects in the immune system. The different PI syndromes are associated with varying degrees of severity, depending on the type of immune defect.² Currently, the World Health Organization (WHO) recognizes approximately 80 distinct PI syndromes.¹ However, the general category of PI includes more than 100 diseases caused by defects of the immune system.

Diagnoses of PI diseases in the U.S. are more prevalent today than previously thought and remain underreported.³ According to data from a population prevalence survey

conducted by the Immune Deficiency Foundation (IDF), approximately 50,000 people in the U.S. were reported to have a PI disease.¹

The frequency of immunodeficiency syndromes varies widely. Rare immune deficiencies, such as severe combined immunodeficiency (SCID), occur in about 1 in 500,000 births;⁴ because of its severity, SCID is diagnosed in the very young. Selective IgA deficiency (SIgAD) is one of the most common PI diseases, with a reported frequency of about 1 in 500 in the general population. Other commonly reported PI diseases include common variable immune deficiency (CVID), IgG subclass deficiency (IgGSD), and X-linked agammaglobulinemia.¹ Both males and females are equally affected by PI diseases.¹

Obtaining an early diagnosis of PI is a substantial clinical challenge. According to a 1996 survey of patients and specialists, sponsored by the Immune Deficiency Foundation (IDF), although a diagnosis was confirmed in 50% of patients before 12 years of age, the diagnosis was not made in approximately 43% of patients until they were adults.¹ Only 12% of patients with a PI disease had initially been found to have a PI before they were one year old.¹ One important reason for late diagnosis is that there is no clear pattern of inheritance: only 2% of PI patients had a father with a PI syndrome, and only 4% had a mother with one of these diseases.¹

Etiology

The human immune system is a complex network of organs, tissues, cells, and protein substances that interact with each other specifically to protect the body from pathogens. Until recently, little was known about the causes of PI diseases. However, this situation has changed with advances in molecular biology and genetics over the past decade. Of the nearly 100 PI diseases that have been identified, approximately two-thirds have been associated with specific molecular defects.⁵ Most of these defects are inherited as recessive traits, several of which are caused by mutations in genes on the X chromosomes and others by mutations on autosomal chromosomes. Many of these disorders have been traced to mutations affecting signaling pathways that dictate immune cell development and their function.⁶

Pathophysiology

Two major categories of immune mechanisms defend the body against infectious or neoplastic disease:

- humoral or antibody-mediated immunity (i.e., B lymphocytes)
- cell-mediated immunity (i.e., T lymphocytes)

Humoral immune response (involving the B cells) includes the production of antibodies that help to control extracellular pathogens.⁷ Disorders of B-cell function, which account for 50% to 60% of PI disorders,⁸ impair a person’s ability to produce antibodies and to defend against microorganisms and toxins that circulate in body fluids or enter the body through the mucosal surface of the respiratory or gastrointestinal (GI) tract. Selective IgA deficiency (IgAD) is the most common B-cell disorder.⁸

T-cell disorders, which account for approximately 5% to 10% of PI diseases,⁸ generally present in infancy or early childhood, and they impair the body’s ability to orchestrate the immune system and to protect against fungal, protozoan, viral, and intracellular bacterial infections. The most common T-cell disorders are DiGeorge syndrome, zeta chain-associated protein kinase 70 (ZAP-70) deficiency, X-linked lymphoproliferative syndrome, and chronic mucocutaneous candidiasis.⁸

Combined T-cell and B-cell immunodeficiency states account for about 20% of PI disorders and affect all aspects of immune function.^{8,9} The most significant form of combined disorders is SCID. In some forms of combined immunodeficiency (e.g., purine nucleoside phos-

phorylase deficiency), Ig levels are normal or elevated, but because of inadequate T-cell function, antibody formation is impaired.⁸

Additional types of PI diseases involve defects in phagocytic cells, natural killer (NK) cells, and complement proteins. Immunodeficiencies are classified according to which part of the immune system is affected.⁸

Table 1 shows the major groups of PI and selective syndromes within them along with the percentage of selective disease within the spectrum.

Clinical Presentation and Evaluation

The clinical presentation of PI depends to an extent on the underlying defect. Most patients with PI disease present with recurrent or chronic infections. Patients with B-cell deficiencies typically present with bacterial infections, whereas patients with combined B-cell and T-cell deficiencies also present with viral or fungal infections.¹⁰ Table 2 identifies important factors in presentation.^{11,12}

Some patients may also present with a variety of other clinical manifestations, including autoimmune or rheumatological disease, or GI complications. In fact, non-infectious manifestations, such as autoimmune disease, may be the first or the predominant clinical symptoms of the underlying immunodeficiency. Other immunodeficiency diseases may be diagnosed because of their known association with syndrome complexes.¹³ For example, children with the DiGeorge syndrome are usually identi-

TABLE 1 Primary Immunodeficiency Groups with Selective Syndromes

Major Group	Selective Syndrome	Percent of Selective Disease Within Spectrum of Primary Deficiency	IVIg Use (Ever)
B-cell (antibody) deficiencies	X-linked agammaglobulinemia	8%	92%
	Common variable immunodeficiency	34%	94%
	Selective IgG deficiency	24%	74%
T-cell deficiencies	DiGeorge anomaly	2%	24%
Combined T-cell and B-cell deficiencies	Severe combined immunodeficiency	4%	80%
Defective phagocytes	Chronic granulomatous disease	4%	12%
Complement deficiencies	Defined by deficient complement	Not reported	Not utilized
Deficiency/cause unknown	Example: hyper-IgE syndrome	Not reported	Not reported

IgE = immunoglobulin E; IgG = immunoglobulin G; IVIg = intravenous immunoglobulin. From Immune Deficiency Foundation, www.primaryimmune.org.¹

fied initially because of the neonatal presentation of congenital heart disease and/or hypocalcemia.¹³ The severity of the deficiency determines the age of presentation, with more severe immunodeficiencies becoming apparent in infancy.¹⁴

According to the Jeffrey Modell Foundation, some warning signs of PI disorders that physicians should look for include:¹⁵

- eight or more new ear infections within a year.
- two or more serious sinus infections within a year.
- two or more months of antibiotic therapy with little effect.
- two or more pneumonias within one year.
- failure of an infant to gain weight or grow normally.
- recurrent, deep skin, or organ abscesses.

- persistent thrush in mouth or elsewhere on skin, after one year of age.
- the need for IV antibiotics to clear infections.
- two or more deep-seated infections.
- a family history of PI.

In addition to an assessment of the type of infectious agent and the location of the infection, an evaluation of a patient thought to have a PI should include a complete patient and family history, a detailed physical examination with pertinent laboratory tests, and diagnostic procedures. The initial screening tests should include a complete blood count (CBC) with differential; quantitative immunoglobulin levels (IgG, IgM, and IgA); specific antibody response to vaccines; IgG subclass analysis; and complement screening.^{14,16} If results to any of these tests are abnormal, further tests are needed to identify specific deficiencies.

TABLE 2 Important Factors in Presentation of Primary Immunodeficiency Diseases*

Group	Onset	Infectious Organism	Other Symptoms
B-cell deficiency	After six months of age, when maternal antibodies decrease; may also present in adulthood	Viral: Enterovirus Bacterial: <i>Streptococcus pneumoniae</i> , <i>Haemophilus influenzae</i> , <i>Staphylococcus aureus</i> , <i>Pseudomonas aeruginosa</i> Fungal and parasitic: <i>Giardia lamblia</i>	Recurrent bacterial infections of the upper and lower respiratory tracts Autoimmune dysfunction
T-cell deficiency and combined deficiency	Before six months of age	Viral: All bacterial: as for B-cell deficiency Fungal and parasitic: Opportunistic infections: <i>Candida albicans</i> , <i>Pneumocystis carinii</i>	Failure to thrive; chronic diarrhea; opportunistic infections
Phagocytic defect	Infancy or childhood	Viral: None Bacterial: <i>S. aureus</i> , enteric flora, <i>P. aeruginosa</i> , <i>Salmonella typhi</i> Fungal and parasitic: <i>Candida</i> spp., <i>Aspergillus</i> spp.	Extreme susceptibility to infections from common pathogens; granulomatous inflammation
Complement deficiency	Any age	Viral: None Bacterial: same as for antibody deficiency, especially <i>Neisseria</i> infections Fungal and parasitic: None	Autoimmune disorders

* Note: The efficacy and safety of Vivaglobin have not been established in children younger than two years of age.

Table based on text from Cooper MA, Pommering TL, Koranyi K. *Am Fam Physician* 2003;68:2001-2008, 2011;¹¹ and Bonilla FA, Geha RS. *J Allergy Clin Immunol* 2003;111:S571-S581.¹²

Current Treatment Options

IMMUNOGLOBULIN REPLACEMENT

The mainstay of therapy for primary immunodeficiency (PI) has been and remains immunoglobulin (Ig) replacement therapy, either by intravenous (IV) infusion or subcutaneous (SQ) injection. The clearest indication for Ig replacement is antibody deficiency. Such deficiencies range from virtually complete absence of all major Ig classes to more selective decreases. The efficacy of Ig replacement therapy in reducing the severity and frequency of infections in PI patients is well established, and it is now recognized that all PI patients who have significantly diminished serum IgG levels who have demonstrated defects in antibody production should receive IgG replacement.^{17,18}

The population prevalence of diagnosed PI in the U.S. is high, approximately 1 in 1,200 people. Yet in a prevalence survey, only a minority of individuals with PI reported being treated with Ig replacement, indicating a serious problem of undertreatment of PI in the general population. In two previous IDF surveys of patients with PI diseases in 1997 and 2003, 70% and 67% of patients, respectively, reported that they were currently being treated with IVIg.^{1,19} However, a 2007 IDF survey indicated that only 22% of patients with PI were then receiving IVIg for their condition.³

ROUTES OF ADMINISTRATION

Immunoglobulin replacement therapy can be given via intramuscular (IM), SQ, and IV routes. The IM route was used commonly until the 1980s, but it is now limited to specialized treatments because of injection-site pain and inconsistent absorption, which makes it difficult to deliver the large doses of Ig required to be therapeutic.²⁰

The most common method of administering Ig in the U.S. is via the IV route; however, this route might not be ideal for all patients. The main limitations of IV administration are (1) difficulty for those with poor venous access, (2) recurrent systemic reactions in some patients, and (3) a requirement for hospitalization or a good-quality home-care program.

Vivaglobin was developed by CSL Behring AG to offer patients with PI an alternative to IVIg therapy, including the option of self-administration with a physician's training and approval. In a multicenter clinical trial conducted in the U.S. and Canada, SQIg was found to be almost as effective as IVIg.

Intravenous Immunoglobulin

At the present time, most patients are treated with IV infusions of Ig preparations.²⁰ IVIg, also called IV gamma

globulin (IVGG), is derived from human blood that has been pooled from 3,000 to 10,000 healthy donors.²⁰ All preparations are subjected to rigorous safety measures, which include screening donors for human immunodeficiency virus (HIV) infection; hepatitis B and C virus (HBV and HCV) infection; and manufacturing procedures that inactivate a wide range of viruses.²⁰ Several standard IVIg products are now available on the U.S. market.

The IV administration of Ig results in an early peak of IgG immediately after the infusion, followed by a slow decline in antibody levels during the days that follow. The half-life of IVIg is usually between 30 and 40 days.²¹⁻²⁵ Common suggested doses range from 400 to 500 mg/kg administered once per month.¹⁷ IVIg products vary in their osmolality and pH, sugar, and sodium content, which can influence patient tolerability and adverse events.²⁶

The incidence of adverse effects with IVIg ranges from 2% to 25% per infusion.²⁷ Hypersensitivity reactions (flushing, dyspnea, anaphylactic reactions) may occur; however, most adverse effects are mild to moderate and transient, including headache, flushing, chills, backache, nausea and vomiting, fever, myalgia, chest tightness, shortness of breath, tachycardia, malaise, dizziness, and hypotension.^{27,28} Reactions usually appear within 15 to 90 minutes after the infusion is started, but they can occur at any time during infusion and may be managed with a decrease in the infusion rate until symptoms subside.^{28,29} Quite often, adverse reactions prolong infusion time.

The mechanism behind the development of reactions has not been fully elucidated but is thought to involve activation of the complement system resulting from the presence of aggregated IgG molecules.³⁰ Mild reactions are commonly managed in most patients with premedications, such as acetaminophen, hydrocortisone, and diphenhydramine, before the infusion is initiated or by lowering the rate of infusion.²⁷ Severe reactions rarely occur.

IVIg has been associated with the development of acute renal failure and renal dysfunction. Based on post-marketing reports, the FDA requires all manufacturers of IVIg to include a boxed warning informing prescribers about the risk of renal dysfunction, acute renal failure, osmotic nephrosis, and death associated with these products. Approximately 88% of the postmarketing reports were associated with products containing sucrose.²⁷

The FDA recommends that physicians evaluate the risks and benefits of administering sucrose-containing products to patients with an increased risk of renal disease, such as those with any degree of pre-existing renal insufficiency, diabetes mellitus, age older than 65, vol-

ume depletion, sepsis, and paraproteinemia, as well as individuals who have received known nephrotoxic drugs. Patients should not be volume-depleted; in patients who are at risk, the minimum concentration and infusion rate should be used. Baseline urine output, blood urea nitrogen, and serum creatinine should also be determined, with monitoring continuing at appropriate intervals.³¹ Other rare adverse events have included aseptic meningitis, thromboembolic events, and transfusion-related acute lung injury (TRALI).²⁷

Based on historical concerns such as renal failure and thrombotic events, patients scheduled to receive Ig therapy should be categorized by degree of risk. Health care professionals managing patients receiving Ig therapy should perform a risk assessment before the initiation of IVIg. Patients with risk factors that may predispose them to renal or thromboembolic adverse events or to aseptic meningitis should be evaluated for the benefits of therapy versus the potential risks.

Depending on the patient's risk factors and infusion-related reactions, the appropriate drug concentration, osmolality, and rate of infusion should be determined. Risk-assessment guidelines are important tools when dosing regimens and routes of administration are being considered. Guidelines include evaluation of the patient's history and physical examination, risk factors, comorbidities, and tolerance to appropriately manage potential adverse events, both serious and nonserious.^{27,31,32}

Subcutaneous Immunoglobulin

Although IVIg has been considered standard first-line therapy for most PI patients in the U.S., SQIg has emerged as an alternative method of administration for both children and adults. In selected patients, SQIg may be preferable to IVIg or IMIg.³³ Advantages of the SQ route include increased patient autonomy, decreased systemic adverse effects, and the lack of a requirement for vascular access.³³ Although SQIg is currently available in the U.S., Vivaglobin is the first product to be approved as safe and effective in the U.S. for this route of administration.

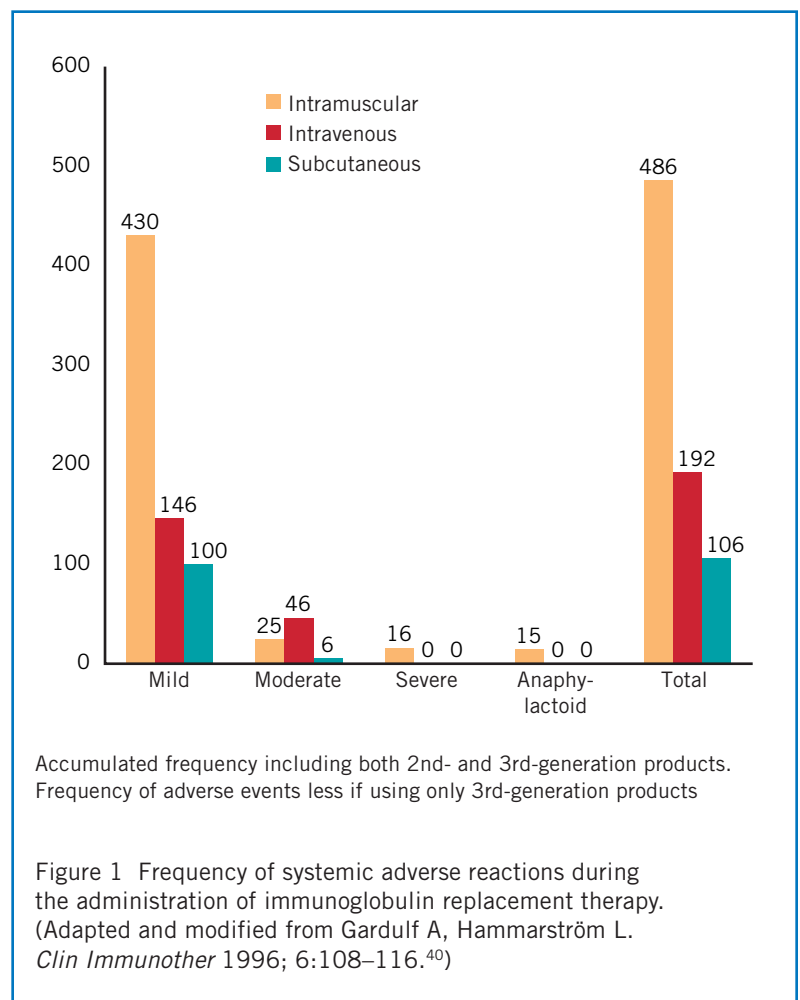
Early studies of SQIg in the 1980s showed that it was associated with fewer adverse effects than IVIg.³⁴⁻³⁶ Berger and colleagues reported giving SQIg a small, portable pump to three patients with common variable immunodeficiency disease (CVID). The SQ infusions were well tolerated, and IgG levels were maintained within the appropriate range.³⁶ In the mid-1990s, there was renewed interest in SQIg using IM or IV products, and

numerous studies and reports evaluating its use have been published.³⁷⁻⁴²

The more frequent and regular dosing of SQIg results in flatter pharmacokinetic (PK) parameters and reduced catabolism of IgG after a large bolus dose.³³ With slow administration and gradual adsorption, the incidence of severe headaches and other adverse events is reduced. Venous access is not necessary, and SQ dosing also facilitates self-infusion or home infusion, thereby increasing patient autonomy with the potential to improve the patient's self-image and sense of control.^{36,38} Published data, mostly from the European experience, equates SQIg with IVIg efficacy for preventing serious bacterial infections.³⁷⁻³⁹ Recent data from the Vivaglobin clinical trials support these historical findings.^{43,44}

Adverse events reported with SQIg consist primarily of local pain or redness at the site of the infusion. From 2.1% to 20% of patients are reported to have experienced these reactions. Systemic effects are less common, with reported rates of 0 to 3.3%.³³ Gardulf and associates published a comparison of the frequency of systemic adverse events during Ig replacement therapy (Figure 1).⁴⁰

SQIg has been used in patients with IgA deficiency with



antibodies against IgA. Severe side effects, including anaphylactoid reactions, have been observed in these patients when they received IV preparations. Eijkhout and coworkers, in a retrospective study, evaluated the use of SQIg in patients with anti-IgA antibodies. A total of 15 patients with IgA deficiency, four of whom had anaphylactoid reactions, were given SQIg using either an IM or IV product. The results showed that even in the presence of anti-IgA antibodies, patients who had reported serious adverse events with previous Ig therapy or transfusions could safely be treated with SQIg.⁴¹

The SQ route of Ig has also been used as home replacement therapy in pregnant women.^{45,46} The route was successfully used in a woman with CVID and splenectomy, as reported by Berger and colleagues in 1982.⁴⁶ Gardulf et al., reporting on the use of the IMIg given subcutaneously to nine women, found that during the course of

pregnancy, IgG and IgG subclass concentrations remained within the normal range.⁴⁵ None of the infants required IgG replacement therapy after delivery. No significant local tissue reactions were noted, and no systemic adverse events attributable to the drug were reported in the more than 400 SQ infusions.⁴⁵

With training, a patient can self-administer Vivaglobin by inserting a catheter, such as a Sof-Set Infusion Set (Medtronic) or Butterfly Infusion Set (Econo-med), beneath the tissue of the abdomen, upper buttocks, lateral thigh, or lateral hip. The patient then prepares Vivaglobin for infusion by drawing up a syringe. The syringe or medication cassette containing Vivaglobin is then loaded into a syringe driver or infusion pump, which is typically small enough to allow the patient to be fully mobile during the infusion.

Chemistry and Pharmacokinetics

PHYSICAL AND CHEMICAL PROPERTIES⁴⁷

Vivaglobin is a polyvalent, liquid, pasteurized human normal immunoglobulin (Ig) preparation designed specifically for subcutaneous (SQ) infusion. This product is composed of native intact IgG molecules that have not undergone enzymatic cleavage or chemical modification. To provide a broad spectrum of antibodies, Vivaglobin is manufactured from large pools of human plasma from healthy, carefully selected donors via a cold alcohol fractionation process.

After concentration of the IgG fraction by cold ethanol precipitation, the fraction is further purified by adsorption with DEAE Sephadex (Sigma-Aldrich) and activated carbon. These adsorbents are removed by depth filtration with a filter aid. The filtrate is pasteurized for 10 hours at 60°C in the presence of the stabilizers glycine and sucrose. The pasteurized solution is clarified and sterile-filtered. The IgG solution is diafiltered to remove the stabilizers and ultra-filtered to prepare it for final formulation.

During production, the risk of potential viral contamination is minimized by ethanol/fatty-alcohol/pH precipitation and pasteurization, both of which are capable of removing or inactivating a broad spectrum of enveloped and non-enveloped viruses.

The active ingredient in IVIg is immunoglobulin G, also known as IgG or gamma globulin, the smallest but most common antibody circulating in the blood. It is a 16% (160-mg/mL) protein solution, with a content of at least 96% IgG, as well as trace amounts of the antibody IgA. The distribution of IgG subclasses is similar to that present in normal human plasma.

Vivaglobin contains 2.25% glycine, 0.3% sodium chloride, and water for injection, USP. The pH of Vivaglobin is 6.4 to 7.2. Vivaglobin contains no preservatives and is free of mercury and latex.

The properties of Vivaglobin are summarized in Table 3 below.

DRUG METABOLISM AND PHARMACOKINETICS⁴⁷

Vivaglobin is administered by injection into SQ tissue. Compared with IV administration, the SQ route results in decreased bioavailability, or approximately 73% of that achieved with IVIg. Various factors, such as the site of administration and IgG catabolism, can also affect absorption. With Vivaglobin administration, peak serum IgG levels are lower than those achieved with IVIg. SQIg results in relatively stable steady-state serum IgG levels when administered on a weekly basis. This serum IgG profile is representative of that seen in a normal population.

Vivaglobin was evaluated in the pharmacokinetic (PK) phase of a pivotal 12-month clinical study conducted in the U.S. and Canada in subjects with PI deficiency (see Clinical Trials, page 10). Subjects who were previously treated with IVIg were switched over to weekly SQ Vivaglobin treatment. After a three-month wash-in/wash-out period, doses were individually adjusted to provide an IgG systemic exposure (area under the curve concentration [AUC]) that was not inferior to the AUC concentration of the previous weekly equivalent IVIg dose.

A Vivaglobin dose of 137% (range, 103%–192%) of the previous weekly equivalent IVIg dose provided a non-inferior AUC concentration. In this study (the North America Study), the geometric mean ratio of the steady-state AUC concentration, standardized to a weekly treatment period, for Vivaglobin, compared with IVIg, was 94.5% (range, 71.4%–110.1%) with a lower 95% confidence limit of 89.8% for the per-protocol population (n = 17).

A six-month, non-IND (Investigational New Drug) clinical study was conducted in Europe and Brazil in 60 subjects with PI disease. After steady state was achieved with weekly Vivaglobin administration, peak serum IgG levels were observed after a mean of 2.5 days (range, 0–7 days) in 41 subjects. In contrast to serum IgG levels observed with monthly IVIg treatment (rapid peaks followed by a slow decline), serum IgG levels in subjects receiving weekly SQ Vivaglobin therapy were relatively stable in both studies.

Table 4 summarizes the PK parameters.

TABLE 3 Physical and Chemical Properties of Vivaglobin

Parameter	Typical Value*
Protein (≥95% IgG)	157–163 mg/mL
IgG monomers and dimers	93%–97%
IgG polymers	3%–5%
IgA	0.39–1.17 mg/mL
HBsAg antibodies	12–55 IU/g Ig
Antibodies to B19 virus	250–300 IU/mL
Diphtheria antitoxin	4–8 IU/ml
Sodium chloride	2.9–3.1 mg/mL
Glycine	22–23 mg/mL
pH	6.7–7.1

IgG = immunoglobulin G; HBsAg = hepatitis B surface antigen.

Data on file, CSL Behring LLC.⁴⁸

TABLE 4 Summary of Additional Pharmacokinetic Parameters: Per-Protocol Subjects

	CE1200_3001 (North America Study)		CE1200_3002 (Europe and Brazil Study)*	
	<i>IVIg</i>	<i>Vivaglobin</i>	<i>IVIg</i>	<i>Vivaglobin</i>
No. of Subjects	17	17	31	41
Dose† Mean Range	120 mg/kg 55–243 mg/kg	165 mg/kg 63–319 mg/kg	NA	95.6 mg/kg 51.1–319 mg/kg
IgG peak levels Mean Range	1,735 mg/dL 1,110–3,230 mg/dL	1,163 mg/dL 743–2,240 mg/dL	NA	910 mg/dL 640–1,520 mg/dL
IgG trough levels Mean Range	883 mg/dL 430–1,600 mg/dL	1,064 mg/dL 54 –2,140 mg/dL	NA	870 mg/dL 600–1,400 mg/dL

* This was the non-Investigational New Drug study.
 † For intravenous immunoglobulin (IVIg): weekly-equivalent dose.
 IgG = immunoglobulin G.
 Data from Vivaglobin prescribing information⁴⁷ and data on file, CSL Behring LLC.⁴⁸

Clinical Trials

Two phase 3 open-label, prospective, multicenter clinical studies were conducted to evaluate the safety, efficacy, and tolerability of Vivaglobin administered subcutaneously to patients with primary immunodeficiency (PI). A pivotal 12-month efficacy study was conducted in the U.S. and Canada (The North America Study), and a prospective, supportive six-month non-IND (Investigational New Drug) trial was conducted in Europe and Brazil.⁴⁸ A total of 125 PI patients between the ages of 3 and 74 years of age were enrolled in the two studies.⁴⁸ Overall, similar rates of serious bacterial infections were noted with Vivaglobin in both studies (Table 5).⁴⁸

NORTH AMERICA STUDY

The North America (NA) Study was performed in three sites in Canada and 16 sites in the U.S. The primary objective was to assess the efficacy via annual serious bacterial infections (i.e., bacterial pneumonia, meningitis, sepsis, osteomyelitis, and visceral abscesses). Secondary endpoints included annual infections and immunoglobulin G (IgG) trough levels. Secondary efficacy parameters included frequency of any infection, frequency of fever, antibiotic use, hospitalizations, lost days from work or school, safety and tolerability. The treatment portion of the trial was a 12-week wash-in/wash-out phase, followed by a 52 (± 2)-week efficacy phase.⁴⁸

Before the start of this study, the pharmacokinetic (PK) parameters were measured to compare the area-under-the-curve (AUC) concentration of IVIg with that of Vivaglobin. A total of 17 patients completed the AUC sampling portion. The retrospective collection of IgG trough levels included two values within the previous two

months.⁴⁸ If one of the values was between 4.5 g/L and 5 g/L, a retrospective collection of all IgG trough levels documented within the previous six months was completed. The subjects were then assessed and doses were adjusted.

A total of 65 adult and pediatric patients with PI who had previously been treated monthly with IVIg were enrolled in the study. Criteria for enrollment required that subjects have a PI syndrome that was further defined in the Europe and Brazil Study as hypogammaglobulinemia or agammaglobulinemia, common variable immune deficiency (CVID), severe combined immunodeficiency (SCID), Wiskott–Aldrich syndrome, Louis–Bar syndrome, or Nijmegen breakage syndrome (also known as Berlin breakage syndrome and Seemanova syndrome). Subjects had to have received IVIg treatment for at least four months before enrollment and had to have a sustained IgG trough concentration of 350 to 450 mg/dL higher than their baseline value or above 500 mg/dL if no baseline value was available.⁴⁸

CVID was diagnosed most frequently (in 68% of patients); congenital hypogammaglobulinemia or agammaglobulinemia was reported as the second most common cause of PI (in 27%). The overall median duration from the time of the diagnosis of PI was approximately 10 years. The median age range was 27 years (range, 3–74 years of age) and 32 patients were 16 years of age or younger.⁴⁸

Because the North America Study was designed to demonstrate non-inferiority to IVIg, subjects in the PK assessment were initially started with a Vivaglobin dose that was 120% of the previous IVIg dose. For the efficacy

TABLE 5 Results from Studies of Vivaglobin Doses, Infections, and Immunoglobulin G (IgG) Levels

	3001 (North America Study) (N = 51)	3002 (Europe and Brazil Study)* (N = 47)
<i>Vivaglobin dose</i>		
Vivaglobin dose as a percentage of IVIg dose	136	101
Mean of the median dose of Vivaglobin (mg/kg)	158	89
<i>Infections</i>		
Annualized rate of serious bacterial infections per subject	0.04	0.04
Annualized rate of any infection/subject	4.4	4.3
<i>IgG levels</i>		
Mean serum IgG level increase during Vivaglobin therapy (mg/dL)	255	86
Vivaglobin mean of the median IgG level	1,040	922

*This was the non-Investigational New Drug study.
IVIg = intravenous immunoglobulin.
Data on file, CSL Behring LLC.⁴⁸

portion of the study, the mean of the median Vivaglobin dose was increased to 137% of the previous IVIg dose, according to the data analysis. Subjects received a mean of the median weekly dose of 158 mg/kg in the efficacy phase.⁴⁸

For the primary efficacy analysis, only two serious bacterial infections (both pneumonia) were reported during the efficacy phase, resulting in an annualized rate of 0.04 serious bacterial infections per subject year. The annualized rate of any infection was 4.4 infections per subject year. Sinusitis and upper respiratory infections were the most frequently reported infections in this study.⁴⁸

Secondary efficacy analyses showed that the annual rate for any kind of infection was 4.43 infectious episodes per subject year, with 88% of mild-to-moderate severity. The annual rate for fever was 0.17 episodes per subject year; the annual hospitalization rate was 0.23 days in the hospital per subject year, and the annual rate for missed school or work attributable to infections was 3.7 days per subject year.⁴⁸

Serum trough IgG concentrations in the efficacy phase were measured as possible surrogate markers against infection and were compared with the infection rate. Although the data showed no general pattern to suggest that higher IgG trough concentrations provided additional protection against infection, the minimum serum concentration of IgG necessary for protection against infections has historically been 500 mg/dL. Serum IgG trough concentrations remained above this level in almost 100% of patients over the course of the study (Table 6).⁴⁸

EUROPE AND BRAZIL STUDY

The primary objective of the non-IND trial was to assess the efficacy of Vivaglobin in patients with PI in terms of IgG trough serum levels. A secondary objective was to evaluate patients' state of health; the frequency, duration, and type of infection; the frequency and duration of febrile episodes; antibiotic use; number of hospitalization days and missed days from school or work; and the agent's safety and tolerability. The PK phase of the study was

designed to measure maximum concentration (C_{max}) and time to maximum concentration (T_{max}) of SQ Vivaglobin.⁴⁸

Enrolled subjects were 3 to 74 years of age with a diagnosis of PI (hypogammaglobulinemia or agammaglobulinemia, CVID, SCID, Wiskott–Aldrich syndrome, Louis-Bar syndrome, or Nijmegen breakage syndrome). They had to have received IVIg or SQIg replacement therapy for at least six months and had to have stable serum IgG trough levels (above 5 g/L) before enrollment. Patients were excluded if they had a history of anaphylactoid reactions to any IgG preparation; severe chronic disease; or known infection with HIV or hepatitis A, B, or C.⁴⁸

A total of 60 patients at 12 study sites in six countries (Austria, Brazil, Germany, Poland, Spain, and Sweden) were invited and agreed to participate. The patients were divided into two age groups: 16 children (2–11 years of age) and 44 adolescents and adults (12 years of age or older). Forty-nine subjects had been receiving IVIg, and 11 subjects had received long-term SQIg replacement therapy with another brand before entering the study.⁴²

Subjects underwent a 16-week wash-in/wash-out phase, then received weekly SQ Vivaglobin infusions in a dose equivalent to their previous IVIg or SCIg dose. Vivaglobin was administered for a total of 43 weeks. For the PK sub-study, the T_{max} and C_{max} were assessed after the wash-in/wash-out phase by following the IgG trough level within one week after the infusion. Subjects were switched to weekly SQ Vivaglobin for six months.⁴⁸

For the PK substudy, the actual mean of median efficacy phase dose was 101%. The mean C_{max} was 73 mg/dL (range, 0–279 mg/dL) above pre-infusion values. The mean T_{max} was 62 hours (range, 11–175 hours) after the infusion start time. The mean of the median dose was 89 mg/kg, which was 101% of the previous weekly equivalent dose.⁴⁸

Forty-seven (47) subjects completed the 12-month primary objective efficacy phase and were included in the per-protocol set efficacy analysis. Evaluation of serum trough IgG concentrations was a primary endpoint in this study.⁴⁸

The per-protocol subjects received a weekly mean Viva-

TABLE 6 North America Study: Secondary Efficacy Phase: (Median Serum Immunoglobulin G (IgG) Trough Concentrations)

<i>Median IgG trough group (mg/dL)</i>	N = 5 ≤700	N = 9 (>700 to ≤900)	N = 37 (>900)
Total number of days in efficacy phase	1,845	3,360	13,744
Total number of infections	32	32	166
Annual rate (infections per subject year)	6.33	3.48	4.41
<i>Median IgG trough concentrations</i>	Mean	Median	SD
Baseline (mg/dL)	786	759	252
Efficacy phase (mg/dL)	1,040	989	272
Difference (mg/dL)	255	235	204

SD = standard deviation.
Data on file, CSL Behring LLC.⁴⁸

TABLE 7 Europe and Brazil Study: Primary Efficacy Phase*

<i>Median IgG trough group (mg/dL)</i>	N = 5 (≤700)	N = 21 (700 to ≤900)	N = 21 (900)
Total number of days in efficacy phase	1,845	3,360	13,744
Total number of infections	8	50	50
Annual rate (infections/subject year)	2.95	4.42	4.39
<i>Median IgG trough concentrations (mg/dL)</i>	Mean	Median	SD
Baseline	837	831	209
Efficacy phase	922	857	223
Difference	86	97	120

SD = standard deviation.

*This was the non-Investigational New Drug study.

Data on file, CSL Behring LLC.⁴⁸

globulin dose of 89 mg/kg of body weight (range, 51–147 mg/kg), which was 101% (range, 81%–146%) of their previous immune globulin treatment. These doses resulted in mean serum IgG level increases from 837 mg/dL to 922 mg/dL. Although the data showed no general pattern to suggest that higher IgG trough concentrations provided additional protection against infection, the minimal amount of IgG required for acceptable protection has historically been 500 mg/dL. Serum IgG trough concentrations remained above this level in almost 100% of patients during the study (Table 7).⁴⁸

For the secondary efficacy analysis, only one serious bacterial infection (pneumonia) was reported during the efficacy phase, resulting in an annualized rate of 0.04 serious bacterial infections per subject year, similar to the North America study. The annualized rate for any infection was also similar to the other study at 4.3 infections per subject year. As in the North America study, sinusitis and upper respiratory infections were the most frequently reported infections in this trial. The annualized rate of hospitalization in this study was 0.47 days hospitalized per subject year, and 26% of participants missed school or work because of infections, for an annualized rate of 10 missed days per subject year.⁴⁸

SUMMARY

Trial Results

Overall, the North America and Europe and Brazil studies demonstrated similar rates of serious bacterial infec-

tions with Vivaglobin regimens, which were 136% and 101%, respectively, of the weekly-equivalent IVIg or SCIG dose from previous treatment (see Table 5). Two serious bacterial infections were reported during the efficacy phase of the North America Study and one was reported in the non-IND Europe and Brazil Study. In the North America study, the rate of serious bacterial infections per subject year was 0.04, and the annual rate for any infection was 4.4 per subject year. The annualized rate of serious bacterial infections in the non-IND study was also 0.04 per subject year, with an annualized rate of any kind of infection of 4.3 per subject year.

In both trials, high serum IgG trough levels were easily maintained after the switch from IVIG to SQIg therapy with the same cumulative monthly dose. These results suggest that SQ administration of IgG is a safe and effective mode of replacement for patients with PI.⁴⁸

Dosing Information

From the IgG serum concentration data utilizing doses, which were an average of 101% or 137% higher than the weekly IVIg dose, it can be concluded that a weekly starting dose of 50 mg/kg to 200 mg/kg would be appropriate to maintain adequate IgG serum concentrations. With this large and loosely defined therapeutic window for immunoglobulins, the importance of individualized dosing for Vivaglobin is apparent. Thus, a range of effective starting doses can be recommended for treating patients with SQ Vivaglobin therapy.⁴⁸

Indications, Dosage, and Administration

INDICATIONS⁴⁷

Vivaglobin is a human normal immunoglobulin designed for subcutaneous (SQ), home-based administration in patients with primary immunodeficiency. Made by CSL Behring LLC, this agent was approved by the FDA in 2006.

DOSAGE AND ADMINISTRATION⁴⁷

Vivaglobin contains no preservative. Therefore, unused product should be discarded immediately after use. Vivaglobin must not be mixed with other medicinal products.

Vivaglobin is to be injected subcutaneously, preferentially in the abdomen, thighs, upper arms, and/or lateral hip.

Dosage

All subjects who received Vivaglobin in the clinical trials had previously been treated with immune globulin. It is recommended that patients start treatment with Vivaglobin one week after receiving a regularly scheduled intravenous immunoglobulin (IVIg) infusion.

The initial weekly Vivaglobin dose can be calculated by multiplying the previous IVIg dose by 1.37, then dividing this dose into weekly doses based on the patient's previous IVIg treatment interval. For example, if IVIg was administered every three weeks, the dose is divided by 3. This dose of Vivaglobin provides a systemic IgG exposure (AUC) comparable to that of the previous IVIg treatment. Weekly administration of this dose leads to stable steady-state serum IgG levels with lower IgG peak levels and higher IgG trough levels compared with monthly IVIg treatment.

The recommended weekly dose of Vivaglobin is 100 to 200 mg/kg of body weight administered subcutaneously. Doses may be adjusted over time to achieve the desired clinical response and serum IgG levels. Because there can be differences in the half-life of IgG among patients with primary immunodeficiency (PI), the dose and dosing interval of immunoglobulin therapy may vary.

Doses and Associated Immunoglobulin G Levels⁴⁷

The minimum serum concentration of IgG necessary for protection against infections has not been established in randomized and controlled clinical studies. However, based on clinical experience, a target serum IgG trough level (i.e., prior to the next infusion) of at least 500 mg/dL has been proposed in the literature for IVIg therapy.

Serum IgG levels can be sampled at any time during routine weekly treatment. Subjects receiving Vivaglobin maintained relatively constant IgG levels rather than the

peak-and-trough pattern observed with monthly IVIg therapy.

Administration⁴⁷

Vivaglobin should not be injected intravenously; it is to be injected subcutaneously, preferably in the abdomen, thighs, upper arms, and/or lateral hip. Vivaglobin must not be injected into a blood vessel.

In the clinical study with Vivaglobin, a volume of 15 mL per injection site at a rate of 20 mL/hour per site was not exceeded. Doses over 15 mL were divided and infused into several sites with the use of an infusion pump. Multiple simultaneous injections were enabled by administration tubing and by Y-site connection tubing. CADD-Legacy pumps (Smiths Medical) were used in the North America Study.

Injection sites were at least two inches apart, and the abdomen, thighs, upper arms, and/or lateral hip were injected with SQ Vivaglobin. The actual point of injection was changed with each weekly administration.

Instructions for Administration⁴⁷

Before the solution is administered, it should be allowed to reach ambient room temperature and should be inspected visually for discoloration and particulate matter prior to administration. The vial should not be shaken. The appearance of Vivaglobin can vary from colorless to light brown. The solution should not be used if it is cloudy, if it has particulates, or if the expiration date on the vial has passed.

Vivaglobin comes with instructions for patients for safe and effective use of the product. These instructions are intended only as a guide. Before self-administering Vivaglobin, patients should be under the care of a physician and should have received training on the proper preparation and administration from a licensed health care provider.

1. Use aseptic technique when preparing and administering Vivaglobin for injection.
2. Remove the protective cap from the vial to expose the central portion of the rubber stopper.
3. Wipe the rubber stopper with alcohol, and allow to dry.
4. Using a sterile syringe and needle, prepare to withdraw Vivaglobin by first injecting air into the vial that is equivalent to the amount of Vivaglobin to be withdrawn.
5. Withdraw the desired amount of Vivaglobin. If multiple vials are required to achieve the desired dose, repeat this step.

6. Follow the manufacturer's instructions for filling the pump reservoir and preparing the pump, administration tubing, and Y-site connection tubing if needed. Prime the administration tubing to ensure that no air is left in the tubing or needle by filling the tubing or needle with Vivaglobin.

7. Select the number and location of injection sites depending on the volume of the total dose. *Note:* In clinical studies with Vivaglobin, a volume of 15 mL per injection site was not exceeded.

8. Clean the injection site with antiseptic solution using a circular motion, working from the center of the site and moving to the outside. Sites should be clean, dry, and at least two inches apart.

9. Grasp the skin between two fingers, and insert the needle into the subcutaneous tissue.

10. Vivaglobin must not be injected into a blood vessel. After each needle is inserted into the tissue, test to make sure that a blood vessel has not been accidentally accessed. This must be done prior to starting the infusion. To do this, attach a sterile syringe to the end of the primed administration tubing, gently pull back on the syringe plunger and check whether any blood is flowing back into the administration tubing.

11. If you see any blood, remove and discard the needle and administration tubing.

12. Repeat the priming and needle insertion steps using a new needle, administration tubing, and a new infusion site. Secure the needle in place by applying sterile gauze or transparent dressing over the site.

13. If using multiple, simultaneous injection sites, use Y-site connection tubing and secure to the administration tubing.

14. Infuse Vivaglobin following the manufacturer's instructions for the pump.

15. Remove the peel-off label with the product lot number and expiration date from the Vivaglobin vial, and use this to complete the patient record.

16. After administration, discard any unused solution and administration equipment in accordance with biohazard procedures.

Home Treatment⁴⁷

If home administration is judged to be appropriate, the physician or health professional should provide the patient with instructions on SQ infusion for home treatment. Directions should include the type of equipment to be used along with its maintenance, proper infusion techniques, selection of appropriate infusion sites (e.g., abdomen, thighs, upper arms, and/or lateral hip), maintenance of a treatment diary, and measures to be taken in case of adverse reactions.

P&T Committee Considerations

Generally speaking, P&T committees must contemplate a number of valid considerations before deciding whether to include or remove a product from the formulary and when developing health plan coverage policies for new therapies. Criteria may include drug safety, efficacy, the need for the agent, potential misuse, side effects, the availability of other agents with similar therapeutic effects, and cost. This section evaluates P&T committee considerations that may apply to Vivaglobin. Included are important measures for product assessment.

EFFICACY⁴⁷

Two phase 3 open-label, prospective, multicenter clinical studies were performed to assess the safety and efficacy of subcutaneous (SQ) Vivaglobin in patients with primary immunodeficiency (PI). The pivotal 12-month efficacy study was conducted in the U.S. and Canada (the North America Study). A supportive six-month non-Investigational New Drug (IND) study was conducted in Europe and Brazil.

The pharmacokinetic (PK) substudy in the North America study was designed to determine the Vivaglobin dose that would provide an area-under-the-curve (AUC) concentration that was non-inferior to the AUC value of IVIg. The Europe and Brazil Study was designed to measure the maximum concentration (C_{max}) and the time to maximum concentration (T_{max}) of SQ Vivaglobin.

The primary efficacy analyses focused on the annual rate of serious bacterial infections and included an assessment of serum IgG trough concentrations. Secondary efficacy parameters included frequency of any infection, frequency of fever, antibiotic use, hospitalizations, lost days from work or school, and safety.

A total of 125 patients with PI between 3 and 74 years of age were enrolled in the two clinical efficacy studies. Because the North America Study was designed to demonstrate non-inferiority to IVIg, subjects in the PK assessment were initially started on a Vivaglobin dose that was 120% of the previous IVIg dose. Based on the data analysis, the mean of the median Vivaglobin dose was increased to 137% of the previous IVIg dose for the efficacy portion of the study. In the non-IND Europe and Brazil Study, the mean of the median Vivaglobin dose used was 101% of the previous IVIg dose for the efficacy phase. These doses resulted in mean serum IgG level increases from 786 mg/dL to 1040 mg/dL in the North America Study and from 837 mg/dL to 922 mg/dL in the Europe and Brazil Study.

For the primary efficacy analysis, only three serious bacterial infections (all pneumonia) were reported dur-

ing the efficacy phase (two in the North America Study and one in the Europe and Brazil Study), resulting in an annualized rate of 0.04 serious bacterial infections per subject year for both studies. The annualized rate of any infection was also similar at 4.4 infections per subject year (North America Study) and 4.3 infections per subject year (Europe and Brazil Study) (see Table 5). Sinusitis and upper respiratory infections were the most frequently reported types in both studies.

Overall, these two studies demonstrated similar rates of serious bacterial infections with Vivaglobin dosing regimens, which were 101% and 137% of the previous IVIg dose.

SAFETY

Contraindications⁴⁷

As with all immune globulin products, Vivaglobin is contraindicated in individuals with a history of anaphylactic or severe systemic response to immune globulin preparations and in persons with selective immunoglobulin A (IgA) deficiency (defined as serum IgA < 0.05 g/L) who have known antibody against IgA.

Warnings⁴⁷

Patients who receive immune globulin therapy for the first time, who are switched from another brand of immune globulin, or who have not received immune globulin therapy within the preceding eight weeks may be at risk for developing reactions that include including fever, chills, nausea, and vomiting. On rare occasions, these reactions may lead to shock. Such patients should be monitored for these reactions in a clinical setting during the initial administration of Vivaglobin.

If anaphylactic or anaphylactoid reactions are suspected, administration should be discontinued immediately. Any acute anaphylactoid reactions should be treated as medically appropriate.

Vivaglobin is made from human plasma. Products made from human plasma may contain infectious agents, such as viruses, that can cause disease. Because Vivaglobin is made from human blood, it may carry a risk of transmitting infectious agents (e.g., viruses) and theoretically, the Creutzfeldt–Jakob agent. The risk that such plasma-derived products will transmit an infectious agent has been reduced by screening plasma donors for prior exposure to certain viruses, by testing for the presence of certain current virus infections, and by inactivating and/or removing certain viruses during manufacture.

Stringent procedures used at plasma collection centers, plasma-testing laboratories, and fractionation facil-

ities are designed to reduce the risk of virus transmission. The primary virus reduction steps of the Vivaglobin manufacturing process are pasteurization (heat treatment of the aqueous solution at 60°C for 10 hours) and ethanol-fatty alcohol/pH precipitation. Additional purification procedures used in the manufacture of Vivaglobin also potentially provide virus reduction.

Despite these measures, such products might still possibly contain human pathogenic agents, including those not yet known or identified. Thus, the risk of transmission of infectious agents cannot be totally eliminated. Any infections thought by a physician to have possibly been transmitted by this product should be reported by the physician or other health care provider to CSL Behring (phone: 800-504-5434 in the U.S. and Canada). The physician should discuss the risks and benefits of this product with the patient.

During clinical trials, no cases of infection attributable to hepatitis A, B, or C virus, Sbb19 isolates, or HIV were reported with the use of Vivaglobin.

Precautions⁴⁷

General. Vivaglobin is intended for subcutaneous (SQ) use. This product should not be administered intravenously. The recommended infusion rate and amount per injection site stated under the Dosage and Administration section should be followed. When initiating therapy with Vivaglobin, patients should be monitored for any adverse events during and after the infusion.

Laboratory tests. After injection of immunoglobulins, the transitory rise of the various passively transferred antibodies in the patient’s blood may yield positive serological testing results, with the potential for misleading interpretation. Passive transmission of antibodies to erythrocyte antigens (e.g., A, B, D) may cause

a positive direct or indirect antiglobulin (Coombs’) test result.

Drug interactions. Immunoglobulin administration can transiently impair the efficacy of live attenuated virus vaccines such as measles, mumps, and rubella. The immunizing physician should be informed of recent therapy with Vivaglobin, so that appropriate precautions can be taken. Vivaglobin should not be mixed with other medicinal products.

Pregnancy Category C. Animal reproduction studies have not been conducted with Vivaglobin. It is also not known whether Vivaglobin can cause fetal harm when administered to a pregnant woman or whether it can affect reproduction capacity. Vivaglobin should be given to a pregnant woman only if it is clearly needed.

Pediatric use. Vivaglobin was evaluated in six children and four adolescents in the U.S. and Canada study and in 16 children and six adolescents in the non-IND study. There were no apparent differences in the safety and efficacy profiles compared with adult subjects. No pediatric-specific dose requirements were necessary to achieve the desired serum IgG levels. The safety and efficacy of Vivaglobin were not studied in pediatric subjects younger than two years of age.

Geriatric use. The clinical study of Vivaglobin did not include sufficient numbers of subjects 65 years of age and older to determine whether they respond differently from younger subjects.

Adverse Reactions⁴⁷

In clinical studies, Vivaglobin has been shown to be safe and well tolerated in both adult and pediatric subjects. Reactions similar to those reported with other immune globulin products may also occur with Vivaglobin. Rarely, immediate anaphylactoid and hypersensitiv-

TABLE 8 Most Frequent Adverse Events (in 10% of Subjects or More) Associated with Vivaglobin Irrespective of Causality*

Adverse Events (≥10% of Subjects)	CE1200_3001 (North America Study) (N = 65)	CE1200_3002 (Europe and Brazil Study)† (N = 60)
	<i>No. of Subjects (Percentage of Total)</i>	
Injection-site reactions	60 (92%)	42 (70%)
Non-injection-site reactions		
Headache	31 (48%)	21 (35%)
Gastrointestinal disorder	24 (37%)	26 (43%)
Fever	16 (25%)	25 (42%)
Nausea	12 (18%)	0
Sore throat	11 (17%)	5 (8%)
Rash	11 (17%)	2 (3%)
Allergic reaction	7 (11%)	5 (8%)

* Excluding infections.

† This was the non-Investigational New Drug study. Data on file, CSL Behring.⁴⁸

TABLE 9 Most Frequent Adverse Events (in 10% of Subjects or More) Associated with Vivaglobin Infusion Irrespective of Causality*

Adverse Events (≥1% of Infusions)	CE1200_3001 (North America Study) (No. of Infusions = 3,656)	CE1200_3002 (Europe and Brazil Study)† (No. of Infusions = 2,297)
	<i>No. of Adverse Events (Rate)‡</i>	
Injection-site reactions	1,789 (49%)	641 (28%)
Mild	1,112 (30%)	626 (27%)
Moderate	601 (16%)	14 (1%)
Severe	65 (2%)	0 (0%)
Unknown severity	11 (< 1%)	1 (<1%)
Non-injection-site reactions		
Headache	159 (4%)	49 (2.1%)
Gastrointestinal disorder	40.3 (1%)§	46 (2%)

* Excluding infections.

† This was the non-Investigational New Drug study.

‡ Rate = number of reactions per infusion.

§ Note: As a result of missing diary information, values listed are estimates. From Vivaglobin prescribing information⁴⁷ and data on file, CSL Behring.⁴⁸

ity reactions may occur. In exceptional cases, sensitization to IgA may result in an anaphylactic reaction (see Contraindications). Should evidence of an acute hypersensitivity reaction be observed, the infusion should be stopped promptly and appropriate treatment and supportive therapy should be administered.

In the U.S. and Canada clinical study, the safety of Vivaglobin was evaluated for 15 months (three-month wash-in/wash-out period followed by a 12-month efficacy period) in 65 subjects with PI. The most frequent adverse reaction was a local reaction at the injection site.

In the non-IND Europe and Brazil study, the safety of Vivaglobin was evaluated for 10 months in 60 subjects with PI disease. The adverse events and their rates reported in this study were similar to those reported in the North America study, with two notable exceptions for the related adverse events. There were 59 episodes of headache (1.6%) and two episodes of fever (0.1%) in the North America Study and no episodes of headache and 18 episodes of fever (0.8%) in the Europe and Brazil study.

Table 8 summarizes the most frequent adverse events by subject reported in the two clinical studies. Table 9 summarizes the most frequent adverse events by infusion.

Local injection-site reactions consisting of mostly mild or moderate swelling, redness and itching, have been observed with the use of Vivaglobin. No serious local site reactions were observed. Most of the injection-site reactions resolved within four days, and the number of patients reporting local injection site reactions decreased substantially after repeated use. Only three subjects in the North America Study and one subject in the other study discontinued therapy because of local injection-site reactions.

CLINICALLY MEANINGFUL ADVANTAGES⁴⁸

Vivaglobin is the only immunoglobulin that has been approved by the FDA for SQ administration, and it offers several advantages over IV products. The use of more stable serum IgG concentrations with fewer peak-and-trough variations provides a serum IgG profile that is representative of that seen in normal immunity.

Vivaglobin is intended for patients with primary immune deficiency who wish to self-administer their immune globulin treatments.

Vivaglobin does not require venous access, thereby maintaining venous integrity, and eliminating infusion nursing services once the patient or caregiver is trained in subcutaneous administration.

Adverse events associated with Vivaglobin are different from those generally attributed to IV immune globulin therapy, and eliminate pre- and post-infusion clinical interventions necessary to manage side effects generally attributed to IVIg products.

Vivaglobin can be safely self-administered in the home, thereby eliminating costs associated with clinic visits and overnight hospital stays.

HOW SUPPLIED⁴⁷

Vivaglobin is supplied in single-use vials containing 160 mg IgG per milliliter. The following dosage forms are available:

- NDC 0053-7596-03, box of 10 3-mL vials
- NDC 0053-7596-10, 10-mL vial
- NDC 0053-7596-15, box of 10 10-mL vials
- NDC 0053-7596-20, 20-mL vial
- NDC 0053-7596-25, box of 10 20-mL vials

STORAGE⁴⁷

Vivaglobin should be stored in the refrigerator at 2° to 8°C (36°–46°F); it should not be frozen. The solution is stable for the period indicated by the expiration date on its label. The vials should be kept in the storage box until use.

The product should be allowed to come to room temperature before it is infused. After the product is opened, the entire bottle should be used and the excess discarded. Partial contents should not be saved for future use.

Conclusion

The subcutaneous, home-based administration of Vivaglobin has proved to be a safe, effective, and convenient option for both adult and pediatric patients with primary immunodeficiency (PI) who require lifelong immunoglobulin (Ig) treatment. Because Vivaglobin offers patients the freedom and flexibility to self-administer this therapy at home, after physician approval and with proper training, it provides a variety of advantages compared with intravenous immunoglobulin (IVIg) products:

- Vivaglobin is the only FDA-approved subcutaneous immune globulin. It is safe and effective for primary immune deficient patients who wish to self-administer immune globulin replacement therapy.
- Vivaglobin is appropriate for patients with difficult venous access.
- Vivaglobin may be an alternative for patients who experience systemic adverse events or require pre-medication with IVIg therapy.
- Vivaglobin eliminates the need for administration at infusion centers or with home nursing.

- Patients can conveniently and safely administer their treatment with a small, portable infusion pump, which allows increased mobility.

The safety and efficacy of SQ Vivaglobin in subjects with PI was assessed in two Phase 3 open-label, prospective, multicenter clinical studies. The pivotal 12-month efficacy study was conducted in the U.S. and Canada, and a supportive six-month non-Investigational New Drug (IND) study was completed in Europe and Brazil. Overall, these two studies demonstrated similar rates of serious bacterial infections with Vivaglobin.

When evaluating Vivaglobin for inclusion in a formulary, P&T committees must consider the product's safety and efficacy, the need for the agent, its potential misuse, side effects, the availability of other agents with similar therapeutic effects, and cost. By reviewing all the facts and making informed decisions about this agent, P&T committees may be able to develop a protocol and categorize patient populations for whom this product may be beneficial.

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Resources

For more information on primary immunodeficiency, readers can visit the Immunodeficiency Foundation's Web site at:

www.primaryimmune.org

Readers can also contact the foundation at:

Immunodeficiency Foundation
40 West Chesapeake Avenue, Suite 308
Towson, MD 21204
1-800-296-4433

idf@primaryimmune.org

For more information on Vivaglobin, readers can visit the CSL Behring Web site at:

www.cslbehring.com

Readers can also contact the company at the following addresses:

Corporate Headquarters

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Vivaglobin® Immune Globulin Subcutaneous (Human)

CSL Behring

Rx only DESCRIPTION

Vivaglobin® Immune Globulin Subcutaneous (Human), is a pasteurized, polyvalent human normal immunoglobulin for subcutaneous infusion. Vivaglobin® is manufactured from large pools of human plasma by cold alcohol fractionation and is not chemically altered or enzymatically degraded.

Vivaglobin® is supplied as a sterile liquid to be administered by the subcutaneous route. Vivaglobin® is a 16% (160 mg/mL) protein solution, with a content of at least 96% immunoglobulin G (IgG). The distribution of IgG subclasses is similar to that present in normal human plasma. Vivaglobin® contains 2.25% glycine, 0.3% sodium chloride, and water for injection, U.S.P. The pH of Vivaglobin® is 6.4 to 7.2. Vivaglobin® contains no preservative.

All plasma used in the manufacture of Vivaglobin® is tested using FDA-licensed serological assays for hepatitis B surface antigen and antibodies to hepatitis C virus (HCV) and human immunodeficiency virus types 1 and 2 (HIV-1/2) as well as FDA-licensed Nucleic Acid Testing (NAT) for HCV and HIV-1 and found to be nonreactive (negative). For hepatitis B virus (HBV), an investigational NAT procedure is used and the plasma found to be negative. However, the significance of a negative result has not been established. In addition, the plasma has been tested by NAT for hepatitis A virus (HAV) and parvovirus B19 (B19). Only plasma that passed virus-screening is used for production and the limit for B19 in the fractionation pool is set not to exceed 10⁴ IU of B19 DNA per mL.

The manufacturing procedure for Vivaglobin® includes multiple processing steps that reduce the risk of virus transmission. The virus reduction capacity of two steps was evaluated in a series of *in vitro* spiking experiments; the steps were ethanol - fatty alcohol / pH precipitation and pasteurization in aqueous solution at 60°C for 10 hours. Total mean cumulative virus reductions ranged from 9.0 to ≥ 14.1 log₁₀, as shown in Table 1.

Table 1: Mean Virus Reduction Factors

Virus Studied:	Ethanol - Fatty Alcohol / pH Precipitation [log ₁₀]	Pasteurization [log ₁₀]	Total Cumulative [log ₁₀]
Enveloped Viruses			
HIV-1	≥ 6.2	≥ 6.5	≥ 12.7
BVDV	≥ 5.3	≥ 8.7	≥ 14.0
WNV	≥ 4.4	≥ 9.3	≥ 13.7
PRV	≥ 6.2	≥ 7.9	≥ 14.1
Non-enveloped Viruses			
PEV	≥ 6.7	3.7	≥ 10.4
CPV	6.7	2.3*	9.0

HIV-1: Human immunodeficiency virus type 1, model for HIV types 1 and 2

BVDV: Bovine viral diarrhoea virus, model for HCV and WNV

WNV: West Nile virus

PRV: Pseudorabies virus, model for large enveloped DNA viruses (e.g., herpes virus)

PEV: Porcine enterovirus, model for HAV (in an immunoglobulin product)

CPV: Canine parvovirus, model for parvovirus B19

* Reduction of parvovirus B19 (evaluated using porcine IgG) by pasteurization was ≥ 3.5 log₁₀.

CLINICAL PHARMACOLOGY

Vivaglobin® Immune Globulin Subcutaneous (Human), supplies a broad spectrum of opsonizing and neutralizing IgG antibodies against a wide variety of bacterial and viral agents.

Vivaglobin® is to be administered by injection into the subcutaneous tissue. Subcutaneous administration of immune globulin decreases bioavailability compared to intravenous administration.¹ The bioavailability of Vivaglobin® is approximately 73% compared to immune globulin intravenous (IGIV). Various factors, such as the site of administration and IgG catabolism, can affect absorption.^{1,2} With Vivaglobin® administration, peak serum IgG levels are lower than those achieved with IGIV. Subcutaneous administration results in relatively stable steady-state serum IgG levels when administered on a weekly basis.^{2,3} This serum IgG profile is representative of that seen in a normal population.

The pharmacokinetics (PK) of Vivaglobin® was evaluated in the PK phase of a pivotal 12-month clinical study conducted in the United States and Canada in subjects with primary immune deficiency (PID) (see **CLINICAL STUDIES**). Subjects who were previously treated with IGIV were switched over to weekly Vivaglobin® subcutaneous treatment and, after a 3-month wash-in/wash-out period, doses were individually adjusted to provide an IgG systemic exposure (area under the curve; AUC) that was not inferior to the AUC of the previous weekly-equivalent IGIV dose. For the 19 per-protocol subjects completing the wash-in/wash-out period, the average Vivaglobin® dose adjustment was 137% (range: 103 to 192%) of the previous weekly-equivalent IGIV dose. Following 10 to 12 weeks of treatment with Vivaglobin® at this adjusted dose, the final steady-state AUC determinations were made. The geometric mean ratio of the steady-state AUCs, standardized to a weekly treatment period, for Vivaglobin® versus IGIV treatment was 94.5% (range: 71.4 to 110.1%) with a lower 95% confidence limit of 89.8% for the per-protocol population (n = 17). Table 2 summarizes additional pharmacokinetic parameters for this study including dosing and serum IgG peak and trough levels following treatment with IGIV and Vivaglobin®.

Table 2: Summary of Additional Pharmacokinetic Parameters – US and Canada PK Sub-study – Per-protocol Subjects

	IGIV	Vivaglobin®
Number of Subjects	17	17
Dose*	Mean Range	Mean Range
	120 mg/kg 55 – 243 mg/kg	165 mg/kg 63 – 319 mg/kg
IgG peak levels	Mean Range	Mean Range
	1735 mg/dL 1110 – 3230 mg/dL	1163 mg/dL 743 – 2240 mg/dL
IgG trough levels	Mean Range	Mean Range
	883 mg/dL 430 – 1600 mg/dL	1064 mg/dL 547 – 2140 mg/dL

* For IGIV: weekly-equivalent dose, † Standardized to a 7-day period

A non-IND 6-month clinical study was conducted in Europe and Brazil in 60 subjects with PID. After the subjects had reached steady state with weekly Vivaglobin® administration, peak serum IgG levels were observed after a mean of 2.5 days (range 0 to 7 days) in 41 subjects.

In contrast to serum IgG levels observed with monthly IGIV treatment (rapid peaks followed by a slow decline), the serum IgG levels in subjects receiving weekly subcutaneous Vivaglobin® therapy were relatively stable in both studies.

CLINICAL STUDIES

The pivotal open-label, prospective, multicenter clinical study conducted in the United States and Canada evaluated the pharmacokinetics, efficacy, safety and tolerability of Vivaglobin® Immune Globulin Subcutaneous (Human), in adult and pediatric subjects with primary immune deficiency (PID). In this study, 65 adult and pediatric PID subjects previously treated monthly with IGIV were switched to weekly subcutaneous administrations of Vivaglobin® for 12 months. The per-protocol efficacy analysis included 51 subjects. Subjects received a weekly mean Vivaglobin® dose of 158 mg/kg body weight (range: 34 to 352 mg/kg), which was 136% (range: 99 to 188%) of their previous weekly-equivalent IGIV dose.

The annual rate of serious bacterial infections (defined as bacterial pneumonia, meningitis, sepsis, osteomyelitis, and visceral abscesses), the primary endpoint, was 0.04 infections per subject per year (one-sided upper 99% confidence interval: 0.14) for the per-protocol set (n = 51). Pneumonia was reported in two subjects. The annual rate of any infections, a secondary endpoint, was 4.4 infections per subject per year.

The IgG subclass levels observed in this study were consistent with a physiologic distribution pattern (mean values) IgG₁: 703 mg/dL, IgG₂: 278 mg/dL, IgG₃: 36 mg/dL, and IgG₄: 30 mg/dL.

Table 3 summarizes the dosing and annual rate of infections for the efficacy phase of this study.

Table 3: Dose and Annual Rate of Infections with Vivaglobin® – Per-protocol Subjects Efficacy Phase of the US and Canada Study

Number of Subjects (Efficacy)	51
Vivaglobin® Dose	
Mean % Previous IGIV Dose (range):	136% (99 – 188%)
Mean:	158 mg/kg b.w.
Range:	34 – 352 mg/kg b.w.
Annual Rate of Serious Bacterial Infections	0.04 infections/subject year
Annual Rate of Any Infections	4.4 infections/subject year

b.w.: body weight

Table 4 provides a summary of missed school or work and hospitalization due to infection, which were secondary endpoints.

Table 4: Summary of Secondary Efficacy Endpoints – Per-protocol Subjects Efficacy Phase of the US and Canada Study

Number of Subjects	51
Total Number of Subject Days	18,949
Total Number of Days Missed School/Work Due to Infection (%)	192 (1.0%)
Annual Rate Missed School/Work Due to Infection (days/subject year)	3.70
Total Number of Days Hospitalized Due to Infection (%)	12 (< 0.1%)
Annual Rate of Hospitalization (days/subject year)	0.23

In a non-IND clinical study of Vivaglobin® conducted in Europe and Brazil, 60 adult and pediatric subjects with PID were switched to weekly subcutaneous administration of Vivaglobin® for six months. Forty-nine (49) subjects had been on IGIV and 11 subjects had been treated long-term with another brand of Immune Globulin Subcutaneous (Human) replacement therapy before entering the study. The forty-seven (47) per-protocol subjects received a weekly mean Vivaglobin® dose of 89 mg/kg body weight (range: 51 to 147 mg/kg), which was 101% (range: 81 to 146%) of their previous immune globulin treatment. The annualized rates of serious bacterial infections (0.04 infections/subject year, one-sided upper 99% confidence interval: 0.21) and any infections (4.3 infections/subject year) were similar to those reported in the study conducted in the US and Canada.

INDICATIONS AND USAGE

Vivaglobin® Immune Globulin Subcutaneous (Human), is indicated for the treatment of patients with primary immune deficiency (PID).

CONTRAINDICATIONS

As with all immune globulin products, Vivaglobin® Immune Globulin Subcutaneous (Human) is contraindicated in individuals with a history of anaphylactic or severe systemic response to immune globulin preparations and in persons with selective immunoglobulin A (IgA) deficiency (serum IgA < 0.05 g/L) who have known antibody against IgA.

WARNINGS

Patients who receive immune globulin therapy for the first time, who are switched from another brand of immune globulin, or who have not received immune globulin therapy within the preceding eight weeks may be at risk for developing reactions including fever, chills, nausea, and vomiting. On rare occasions, these reactions may lead to shock. Such patients should be monitored for these reactions in a clinical setting during the initial administration of Vivaglobin® Immune Globulin Subcutaneous (Human).

If anaphylactic or anaphylactoid reactions are suspected, discontinue administration immediately. Treat any acute anaphylactoid reactions as medically appropriate.

Vivaglobin® is made from human plasma. Products made from human plasma may contain infectious agents, such as viruses, that can cause disease. Because Vivaglobin® is made from human blood, it may carry a risk of transmitting infectious agents, e.g., viruses, and theoretically, the CJD agent. The risk that such plasma-derived products will transmit an infectious agent has been reduced by screening plasma donors for prior exposure to certain viruses, by testing for the presence of certain current virus infections, and by inactivating and/or removing certain viruses during manufacture (see **DESCRIPTION** section for virus reduction measures). Stringent procedures utilized at plasma collection centers, plasma-testing laboratories and fractionation facilities are designed to reduce the risk of virus transmission. The primary virus reduction steps of the Vivaglobin® manufacturing process are pasteurization (heat treatment of the aqueous solution at 60°C for 10 hours) and ethanol - fatty alcohol / pH precipitation. Additional purification procedures used in the manufacture of Vivaglobin® also potentially provide virus reduction. Despite these measures, such products may still potentially contain human pathogenic agents, including those not yet known or identified. Thus, the risk of transmission of infectious agents cannot be totally eliminated. Any infections though by a physician to have been possibly transmitted by this product should be reported by the physician or other healthcare provider to CSL Behring at 1-800-504-5434 (in the US and Canada). The physician should discuss the risks and benefits of this product with the patient.

During clinical trials, no cases of infection due to hepatitis A, B, or C virus, parvovirus B19, or HIV were reported with the use of Vivaglobin®.

PRECAUTIONS

General-Administer Vivaglobin® Immune Globulin Subcutaneous (Human), subcutaneously. Do not administer this product intravenously. The recommended infusion rate and amount per injection site stated under **DOSAGE AND ADMINISTRATION** should be followed. When initiating therapy with Vivaglobin®, patients should be monitored for any adverse events during and after the infusion.

Laboratory Tests - After injection of immunoglobulins, the transitory rise of the various passively transferred antibodies in the patient's blood may yield positive serological testing results, with the potential for misleading interpretation. Passive transmission of antibodies to erythrocyte antigens, e.g., A, B, D may cause a positive direct or indirect antiglobulin (Coombs') test.

Drug Interactions - Immunoglobulin administration can transiently impair the efficacy of live attenuated virus vaccines such as measles, mumps and rubella. The immunizing physician should be informed of recent therapy with Vivaglobin® Immune Globulin Subcutaneous (Human), so that appropriate precautions can be taken.

Vivaglobin® should not be mixed with other medicinal products.

Pregnancy Category C - Animal reproduction studies have not been conducted with Vivaglobin® Immune Globulin Subcutaneous (Human). It is also not known whether Vivaglobin® can cause fetal harm when administered to a pregnant woman, or can affect reproduction capacity. Vivaglobin® should be given to a pregnant woman only if clearly needed.

Pediatric Use - Vivaglobin® was evaluated in 6 children and 4 adolescents in the US and Canada study and in 16 children and 6 adolescents in the non-IND study. There were no apparent differences in the safety and efficacy profiles as compared to adult subjects. No pediatric-specific dose requirements were necessary to achieve the desired serum IgG levels. The safety and efficacy of Vivaglobin® was not studied in pediatric subjects under two years of age.

Geriatric Use - The clinical study of Vivaglobin® Immune Globulin Subcutaneous (Human), did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects.

ADVERSE REACTIONS

In clinical studies, administration of Vivaglobin® Immune Globulin Subcutaneous (Human), has been shown to be safe and well tolerated in both adult and pediatric subjects. Reactions similar to those reported with administration of other immune globulin products may also occur with Vivaglobin®. Rarely, immediate anaphylactoid and hypersensitivity reactions may occur. In exceptional cases, sensitization to IgA may result in an anaphylactoid reaction (see **CONTRAINDICATIONS**).

Should evidence of an acute hypersensitivity reaction be observed, the infusion should be stopped promptly, and appropriate treatment and supportive therapy should be administered.

In the US and Canada clinical study, the safety of Vivaglobin® was evaluated for 15 months (3-month wash-in/wash-out period followed by 12-month efficacy period) in 65 subjects with PID. The most frequent adverse reaction was local reaction at the injection site. Table 5 summarizes the most frequent adverse events by subject reported in the clinical study, and Table 6 summarizes the most frequent adverse events by infusion.

Table 5: Most Frequent Adverse Events by Subject Irrespective of Causality[†] in the US and Canada Study

Adverse Events (≥ 10% of subjects)	No. of Subjects (% of total)
Adverse Events at the Injection Site	60 (92%)
Non-Injection Site Reactions	
Headache	31 (48%)
Gastrointestinal disorder	24 (37%)
Fever	16 (25%)
Nausea	12 (18%)
Sore throat	11 (17%)
Rash	11 (17%)
Allergic reaction	7 (11%)
Pain	6.7 (10%) [†]
Diarrhea	6.7 (10%) [†]
Cough increased	6.7 (10%) [†]

[†] Excluding infections

[†] Due to missing subject diary information, values listed are estimates.

Table 6: Most Frequent Adverse Events by Infusion Irrespective of Causality* in the US and Canada Study

Adverse Events (≥ 1% of infusions) (Number of Infusions: 3656)	No. of Adverse Events (Rate**)
Adverse Events at the Injection Site	1789 (49%)
Mild	1112 (30%)
Moderate	601 (16%)
Severe	65 (2%)
Unknown Severity	11 (< 1%)
Non-Injection Site Reactions	159 (4%)
Headache	40.3 (1%)†
Gastrointestinal disorder	

*Excluding infections
 **Rate = number of reactions/infusion
 †Due to missing subject diary information, values listed are estimates.

Table 7 summarizes the most frequent related adverse events by subject reported in the clinical study, and Table 8 summarizes the most frequent related adverse events by infusion.

Table 7: Most Frequent Related Adverse Events by Subject* in the US and Canada Study

Related Adverse Event (≥ 2 subjects)	No. of Subjects (% of total)
Adverse Events at the Injection Site	60 (92%)
Non-Injection Site Reactions	
Headache	21 (32%)
Nausea	7 (11%)
Rash	4 (6%)
Asthenia	3 (5%)
Gastrointestinal disorder	3 (5%)
Fever	2 (3%)
Skin disorder	2 (3%)
Tachycardia	2 (3%)
Urine abnormality	2 (3%)

*Excluding infections

Table 8: Most Frequent Related Adverse Events by Infusion* in the US and Canada Study

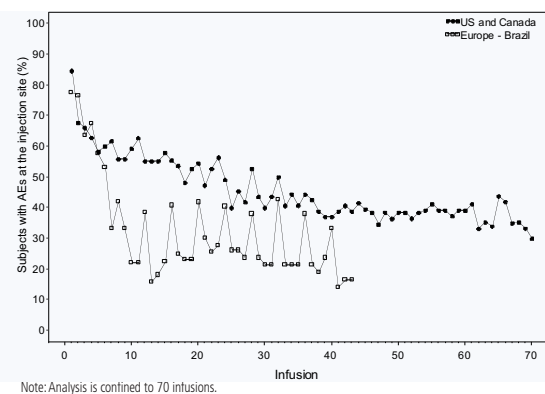
Related Adverse Event (≥ 2 AEs) (Number of Infusions: 3656)	No. of AEs (Rate**)
Adverse Events at the Injection Site	1787 (49%)
Non-Injection Site Reactions	
Headache	59 (1.6%)
Rash	9 (0.2%)
Nausea	9 (0.2%)
Nervousness	4 (0.1%)
Asthenia	3 (0.1%)
Gastrointestinal disorder	3 (0.1%)
Skin disorder	3 (0.1%)
Urine abnormality	3 (0.1%)
Fever	2 (0.1%)
Dyspnea	2 (0.1%)
Gastrointestinal pain	2 (0.1%)
Tachycardia	2 (0.1%)

*Excluding infections
 **Rate = number of reactions/infusion

In the non-IND Europe and Brazil clinical study, the safety of Immune Globulin Subcutaneous (Human), Vivaglobin® was evaluated for 10 months in 60 subjects with PID. The adverse events and their rates reported in this study were similar to those reported in the US and Canada study, with two notable exceptions for the related adverse events. These events were 59 episodes of headache (1.6%) and 2 episodes of fever (0.1%) in the US and Canada study and no episodes of headache and 18 episodes of fever (0.8%) in the Europe and Brazil study.

Local (Injection Site) Reactions - Local injection site reactions consisting of mostly mild or moderate swelling, redness and itching, have been observed with the use of Vivaglobin®. No serious local site reactions were observed. The majority of injection site reactions resolved within four days. Additionally, the number of subjects reporting local injection site reactions decreased substantially after repeated use (see Figure 1). Only three subjects in the US and Canada study and one subject in the Europe and Brazil study discontinued due to local site reactions.

Figure 1: Subjects Reporting Local Site Reactions By Infusion



DOSE AND ADMINISTRATION

Vivaglobin® Immune Globulin Subcutaneous (Human), contains no preservative. Therefore, discard unused product immediately after use.
 Vivaglobin® must not be mixed with other products.
 Vivaglobin® is to be injected subcutaneously, preferentially in the abdomen, thighs, upper arms, and/or lateral hip.

DO NOT INJECT INTO A BLOOD VESSEL.

Dosage
 All subjects who received Vivaglobin® in the clinical trials had previously been treated with immune globulin. It is recommended that the patient start treatment with Vivaglobin® one week after receiving a regularly scheduled IGIV infusion.

The initial weekly Vivaglobin® dose can be calculated by multiplying the previous IGIV dose by 1.37, then dividing this dose into weekly doses based on the patient's previous IGIV treatment interval; for example, if IGIV was administered every three weeks, divide by 3. This dose of Vivaglobin® will provide a systemic IgG exposure (AUC) comparable to that of the previous IGIV treatment. Weekly administration of this dose will lead to stable steady-state serum IgG levels with lower IgG peak levels and higher IgG trough levels compared to monthly IGIV treatment (see Table 2 for trough levels).

The recommended weekly dose of Vivaglobin® is 100 to 200 mg/kg body weight administered subcutaneously. Doses may be adjusted over time to achieve the desired clinical response and serum IgG levels. As there can be differences in the half-life of IgG among patients with primary immune deficiencies, the dose and dosing interval of immunoglobulin therapy may vary.

Doses And Associated IgG Levels

The minimum serum concentration of IgG necessary for protection against infections has not been established in randomized and controlled clinical studies. However, based on clinical experience, a target serum IgG trough level (i.e., prior to the next infusion) of at least 500 mg/dL has been proposed in the literature for IGIV therapy.

Serum IgG levels can be sampled at any time during routine weekly treatment. Subjects on Immune Globulin Subcutaneous (Human), Vivaglobin® therapy maintained relatively constant IgG levels, rather than the peak and trough pattern observed with monthly IGIV therapy.

Administration

DO NOT INJECT INTRAVENOUSLY.

In the clinical study with Vivaglobin®, a volume of 15 mL per injection site at a rate of 20 mL per hour per site was not exceeded. Doses over 15 mL were divided and infused into several sites using an infusion pump. Multiple simultaneous injections were enabled by administration tubing and Y-site connection tubing (CADD-Legacy® pumps were used in the study conducted in the US and Canada). Injection sites were at least two inches apart.

The following areas were used for subcutaneous injection of Vivaglobin®: abdomen, thighs, upper arms, and/or lateral hip. The actual point of injection was changed with each weekly administration.

Instructions for Administration

Prior to use, allow the solution to reach ambient room temperature. Vivaglobin® should be inspected visually for discoloration and particulate matter prior to administration. DO NOT SHAKE. The appearance of Vivaglobin® can vary from colorless to light brown. Do not use if the solution is cloudy or has particulates. Check the product expiration date on the vial. Do not use beyond the expiration date.

- Use aseptic technique when preparing and administering Vivaglobin® for injection.
- Remove the protective cap from the vial to expose the central portion of the rubber stopper.
- Wipe the rubber stopper with alcohol and allow to dry.
- Using a sterile syringe and needle, prepare to withdraw Vivaglobin® by first injecting air into the vial that is equivalent to the amount of Vivaglobin® to be withdrawn. Then withdraw the desired volume of Vivaglobin®. If multiple vials are required to achieve the desired dose, repeat this step. (Fig. 2)
- Follow the manufacturer's instructions for filling the pump reservoir and preparing the pump, administration tubing and Y-site connection tubing, if needed. Be sure to prime the administration tubing to ensure that no air is left in the tubing or needle by filling the tubing/needle with Vivaglobin®.
- Select the number and location of injection sites depending on the volume of the total dose. Note: In clinical studies with Vivaglobin®, a volume of 15 mL per injection site was not exceeded. (Fig. 3)
- Cleanse the injection site(s) with antiseptic solution using a circular motion working from the center of the site and moving to the outside. Sites should be clean, dry, and at least two inches apart. (Fig. 4)
- Grasp the skin between two fingers and insert the needle into the subcutaneous tissue. (Fig. 5)
- Vivaglobin® must **not** be injected into a blood vessel. After each needle is inserted into the tissue, test to make sure that a blood vessel has not been accidentally accessed. This must be done prior to starting the infusion. To do this, attach a sterile syringe to the end of the primed administration tubing, gently pull back on the syringe plunger and look to see if any blood is flowing back into the administration tubing. If you see any blood, remove and discard the needle and administration tubing. Repeat priming and needle insertion steps using a new needle, administration tubing and a new infusion site. Secure the needle in place by applying sterile gauze or transparent dressing over the site. (Fig. 6)
- If using multiple, simultaneous injection sites, use Y-site connection tubing and secure to the administration tubing.
- Infuse Vivaglobin® following the manufacturer's instructions for the pump. (Fig. 7)
- Remove the peel-off label with the product lot number and expiration date from the Vivaglobin® vial and use this to complete the patient record.



Fig. 2

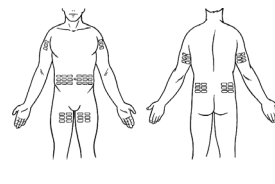


Fig. 3

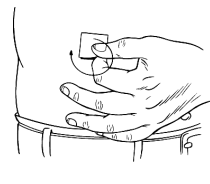


Fig. 4

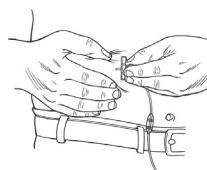


Fig. 5

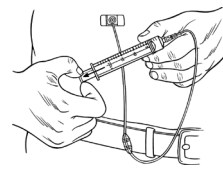


Fig. 6

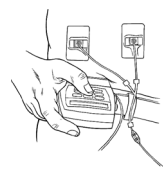


Fig. 7

After administration, discard any unused solution and administration equipment in accordance with biohazard procedures.

Home Treatment

If the physician believes that home administration is appropriate, the physician or health professional should provide the patient with instructions on subcutaneous infusion for home treatment. This should include the type of equipment to be used along with its maintenance, proper infusion techniques, selection of appropriate infusion sites (e.g., abdomen, thighs, upper arms, and/or lateral hip), maintenance of a treatment diary, and measures to be taken in case of adverse reactions.

HOW SUPPLIED

Vivaglobin® Immune Globulin Subcutaneous (Human), is supplied in single-use vials containing 160 mg IgG per mL. The following dosage forms are available:

- NDC 0053-7596-03 Box of ten 3 mL vials
- NDC 0053-7596-10 10 mL vial
- NDC 0053-7596-15 Box of ten 10 mL vials
- NDC 0053-7596-20 20 mL vial
- NDC 0053-7596-25 Box of ten 20 mL vials

STORAGE

Store in the refrigerator at 2 - 8°C (36 - 46°F). Vivaglobin® Immune Globulin Subcutaneous (Human), is stable for the period indicated by the expiration date on its label. Do not freeze. Keep vials in storage box until use.

REFERENCES

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- Waniewski I, Gardulf A, Hammarström L. Bioavailability of Y-Globulin after subcutaneous infusions in patients with common variable immunodeficiency. *J Clin Immunol* 1994;14(2):90-7.
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Vivaglobin[®]

Immune Globulin Subcutaneous (Human)

[Pronounced VEE-vah-glow-bin]



CSL Behring Information for patients

This summary contains important information you need to know about Vivaglobin[®] for treating primary immunodeficiency (also known by its abbreviation, "PID"). *Please read it carefully before you start your treatment.* This summary is based on information given to your doctor but does not include all available information about Vivaglobin[®]. The summary is not meant to take the place of your doctor's instructions and should be used only after you have received instructions from your doctor. You should discuss any questions about treatment with Vivaglobin[®] with your doctor.

What is Vivaglobin[®]?

Vivaglobin[®] is a highly purified product, called an immune globulin, made from human plasma. Vivaglobin[®] contains the antibody immunoglobulin G (IgG), which is found in the blood of healthy individuals to help combat germs, such as bacteria and viruses. Because it helps the body rid itself of these bacteria and viruses, IgG is important in helping the body fight infection.

Vivaglobin[®] also contains the following inactive ingredients: 2.25% glycine, 0.3% sodium chloride, and water for injection.

What is Vivaglobin[®] used for?

Vivaglobin[®] is a prescription medication used to treat patients with primary immunodeficiency.

Vivaglobin[®] is supplied as a sterile liquid in single-use vials and is given by infusion subcutaneously (under the skin). **Do not administer Vivaglobin[®] into a blood vessel (vein or artery) as there is no safety information in patients supporting this route of administration.**

For treatment to be effective, you must carefully follow your doctor's instructions regarding your dose and treatment schedule for Vivaglobin[®].

How does Vivaglobin[®] work?

Vivaglobin[®] treats primary immunodeficiency, a condition in which a person's natural defense system – or immune system – does not function properly.

Normally, our immune system helps protect us against infections by recognizing potentially harmful bacteria and viruses that enter our body every day. In response, the immune system produces special proteins called antibodies that fight these foreign invaders. However, when our immune system is not working properly, it is unable to produce these valuable antibodies, leaving us more vulnerable to infection and illness.

Vivaglobin[®] is known as antibody replacement therapy, because it replaces the missing and much-needed IgG antibodies in people who have low levels of this infection-fighting protein. By replacing these important antibodies, Vivaglobin[®] helps make people with PID better able to avoid infections and fight them when they do occur.

Who should **NOT** take Vivaglobin[®]?

People who have a history of allergic reactions to immunoglobulins or have a condition known as selective IgA deficiency should not use Vivaglobin[®]. Tell your doctor if you have ever had an allergic reaction due to either of these conditions. If a serious allergic reaction occurs at any time, stop the Vivaglobin[®] treatment and contact your doctor or an emergency medical professional immediately.

Because clinical studies with pregnant women have not been conducted, if you are pregnant or think you may be pregnant, discuss with your doctor whether Vivaglobin[®] is clearly needed. Please also consult your doctor about the use of this product if you are a nursing mother.

What are possible side effects of Vivaglobin[®]?

In clinical studies, Vivaglobin[®] has been shown to be safe and well tolerated in both adults and children. As with any medication, side effects may accompany treatment.

The frequency of side effects was based on a review of over 5,900 injections given during the clinical trials. The most frequently reported side effect was injection site reaction, which generally consisted of mild or moderate swelling, redness, and itching at the site of injection. In clinical trials, these reactions tended to decrease substantially over time. Please contact your healthcare provider if you would like more information on managing these reactions.

Other side effects may include:

- Headache
- Gastrointestinal disorder
- Fever
- Nausea
- Sore throat
- Rash
- Allergic reaction
- Increased cough
- Pain
- Diarrhea

If you are concerned about these or any other side effects, please talk to your healthcare provider.

What additional important information do I need to know about Vivaglobin[®]?

Immune Globulin Subcutaneous (Human) Vivaglobin[®] is made from the plasma portion of human blood. All plasma used to produce Vivaglobin[®] is collected in a manner that meets or exceeds U.S. Food and Drug Administration requirements. For your safety, we maintain stringent controls over plasma collection and processing every step of the way. Because Vivaglobin[®] is made from plasma, as are all immune globulins, the risk of transmitting infectious agents, including viruses, and theoretically, the Creutzfeldt-Jakob Disease (CJD) agent, cannot be completely eliminated. However, the risk that Vivaglobin[®] will transmit diseases is reduced by carefully screening plasma donors for prior exposure to certain viruses and by testing plasma for evidence of potentially harmful viruses. Only plasma that passed virus-screening is used for production of Vivaglobin[®].

During the manufacture of Vivaglobin[®], specific viral clearance methods further decrease the chance of disease transmission. The main virus reduction step of the Vivaglobin[®] manufacturing process is a pasteurization technique, which involves heating the product at 140°F (60°C) for 10 hours. Additional purification procedures used in the manufacture of Vivaglobin[®] further reduce the risk of disease. As with all products manufactured from human plasma, however, the risk of transmitting infectious agents cannot completely be eliminated. However, during clinical trials, no cases of infection due to hepatitis A, B, or C virus, parvovirus B19, or HIV were reported with the use of Vivaglobin[®]. If you believe that you have contracted an infection that was possibly transmitted by Vivaglobin[®], you should report this to your doctor or healthcare provider.

What medications should I avoid while taking Vivaglobin[®]?

Vivaglobin[®] can impair the efficacy of certain virus vaccines, such as measles, mumps and rubella (also known by its abbreviation "MMR"). Inform the immunizing physician of recent treatment with Vivaglobin[®] so appropriate precautions can be taken.

Other products must not be mixed with the Vivaglobin[®] solution.

How do I store Vivaglobin[®]?

Vivaglobin[®] is supplied in single-use vials. It contains no preservatives, so any unused portion should be discarded immediately after use. When stored in the refrigerator at 36° to 46°F (2° to 8°C) Vivaglobin[®] can be used until the expiration date on its label. Do not use after the expiration date. *Do not freeze Vivaglobin[®].* Keep the vial in its box during storage. Keep Vivaglobin[®] and all other medications out of the reach of children.

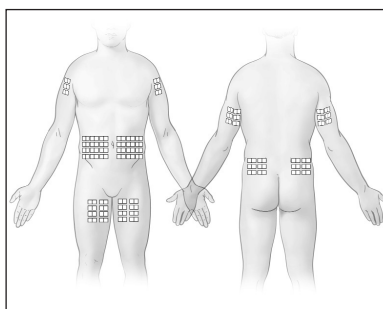
How do I use Vivaglobin[®]?

Vivaglobin[®] is infused subcutaneously (under the skin). Do not administer it into a blood vessel (vein or artery).

Your doctor will determine the appropriate dose for your treatment.

Your doctor or healthcare provider will teach you the proper techniques for administering Vivaglobin[®]. **Only after such instruction should you follow the instructions below.**

Preparing for your treatment



The following areas are recommended for subcutaneous infusion of Vivaglobin[®]:

- Abdomen
- Thighs
- Upper arms
- Hip

For proper selection of infusion site, please consult your doctor or healthcare provider.

Instructions for administration

The following instructions are intended only as a guide. Before administering Vivaglobin® Immune Globulin Subcutaneous (Human) you should be under the care of a doctor and should have received proper training on proper preparation and administration from a licensed healthcare provider.



Fig. 1

1. Prior to use, allow the vial(s) of Vivaglobin® to reach room temperature, 68° to 77°F (20° to 25°C). On a clean, flat surface, such as a table, assemble all the supplies you will need for your treatment, including Vivaglobin® vials, treatment diary/logbook, an infusion pump, administration tubing, subcutaneous needle or catheter, Y-site connection tubing (if needed), alcohol wipes, antiseptic skin preps, syringe(s), needle(s), gauze or transparent dressing, tape and a sharps disposal container. Your healthcare provider can help you to identify a complete list of supplies. Discuss with your healthcare provider whether you should use gloves when preparing Vivaglobin® for infusion. (Fig. 1)

2. There are several different types of ambulatory infusion pumps that may be used to administer Vivaglobin®. Your healthcare provider will help you to determine which type of pump is appropriate for you. Follow the pump manufacturer's instructions for preparing the infusion pump and priming the administration tubing. Set the rate of infusion on the pump as instructed by your healthcare provider.

3. Before preparing Vivaglobin® for infusion, thoroughly wash and dry your hands. (Fig. 2)

4. Before each infusion, be sure to visually inspect each vial of Vivaglobin® for discoloration and for particles in the solution by gently swirling each vial (do **not** shake the vial). Vivaglobin® should be a clear solution that can vary from colorless to light brown. If the solution in a vial is cloudy or contains particles, or if the protective cap is missing, do not use it. Check the expiration date on each vial of Vivaglobin®. Do not use beyond the expiration date. (Fig. 3)

5. Remove the protective cap from each vial of Vivaglobin®. Next, cleanse the top of each vial stopper with an alcohol wipe, and allow the top of the vial to dry. (Figs. 4 and 5)

6. Using aseptic technique as instructed by your healthcare provider, attach a needle to the syringe tip. (Fig. 6)

7. Pulling back on the syringe plunger, draw back a volume of air into the syringe that is equal to the volume of Vivaglobin® that will be withdrawn. With the Vivaglobin® vial placed on a flat surface, insert the needle into the center of the vial stopper. Then inject the air into the vial. Next, leaving the syringe and needle in the vial, carefully invert the vial as shown in the illustration. Withdraw the Vivaglobin® solution into the syringe and remove the filled syringe from the vial. Remove the needle from the syringe filled with Vivaglobin® and discard the needle into a sharps disposal container. Repeat this step if multiple vials are required to achieve the prescribed dose of Vivaglobin®. (Fig. 7)

8. Follow manufacturer's instructions for filling the infusion pump reservoir and priming the administration tubing and needle/catheter. "Priming" the administration tubing refers to the removal of the air from the tubing and needle/catheter that will be used to infuse Vivaglobin®. Priming may also be done by connecting the syringe filled with Vivaglobin® to the administration tubing and gently pushing on the syringe plunger to fill the tubing with Vivaglobin® until a drop is seen exiting the needle/catheter. (Fig. 8)

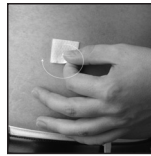


Fig. 9



Fig. 10



Fig. 11

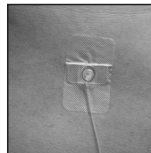


Fig. 12



Fig. 13



Fig. 14



Fig. 15

9. Select an appropriate infusion site(s), depending on the amount required for your total Immune Globulin Subcutaneous (Human) Vivaglobin® dose and the instructions of your healthcare provider. Cleanse the site(s) with antiseptic skin prep(s) beginning in the center of the site and working outward in a circular motion. Allow site(s) to dry before proceeding to the next step. If your healthcare provider recommends that you administer Vivaglobin® using multiple sites, ensure that each site is at least two inches apart. (The maximum recommended infusion volume per infusion site is 15 mL). (Fig. 9)

10. Using two fingers, grasp the skin around the infusion site. As instructed by your healthcare provider, insert the needle directly into the subcutaneous tissue and **not** into a blood vessel. (Fig. 10)

11. After each needle is inserted into the tissue, you must test to make sure that a blood vessel has not been accidentally entered. This must be done prior to starting your infusion. To do this attach a sterile syringe to the end of the primed administration tubing, and gently pull back on the syringe plunger. Look to see if any blood is flowing back into the administration tubing. If you see any blood, remove and discard the needle and administration tubing. Then, repeat steps 8–11 using a new needle, administration tubing and a new infusion site. (Fig. 11)

12. Secure the needle by applying sterile gauze or transparent dressing over the site and tape in place. (Fig. 12)

13. Secure the administration tubing to the infusion pump following the manufacturer's instructions and turn on the pump. (Fig. 13)

14. Once the infusion is complete, turn off the infusion pump. Remove the needle(s) from the infusion site(s) and discard any unused solution and administration equipment in accordance with biohazard procedures as recommended by your healthcare provider. Follow the manufacturer's instructions regarding care of the infusion pump after each use. (Fig. 14)

15. On each Vivaglobin® vial, you will find a peel-off label with the product lot number and expiration date. Record the time, date, and exact dose of your infusion, then remove the labels and affix them to your treatment diary/logbook. Take this record of your treatment with you whenever you visit your physician. (Fig. 15)

These instructions are intended to serve as a guide for people who have already been instructed by a healthcare professional on the proper method of preparing and administering Vivaglobin®. If you have not received such training, please consult your healthcare provider before attempting to administer Vivaglobin®. If you experience any problems or need more information regarding your subcutaneous treatment, contact your healthcare provider.

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