PRODUCT MONOGRAPH

Vivaglobin®

Immune Globulin Subcutaneous (Human)

16% Protein Solution (160 mg/mL)

Passive Immunizing Agent

CSL Behring Canada, Inc.
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Vivaglobin®

Immune Globulin Subcutaneous (Human)

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Subcutaneous	Solution for subcutaneous infusion ≥ 96 % IgG	Glycine, sodium chloride *For a complete listing of the nonmedicinal ingredients, see Product Characteristics.*

DESCRIPTION

Vivaglobin® Immune Globulin Subcutaneous (Human), is a pasteurized, polyvalent human normal immunoglobulin for subcutaneous infusion. Vivaglobin® consists of a 16% protein solution in 22.5 mg/ml glycine, 0.3% sodium chloride, and water for injection U.S.P. Vivaglobin® is manufactured from large pools of human plasma by cold alcohol fractionation and is not chemically altered or enzymatically degraded. Vivaglobin® contains no preservative.

INDICATIONS AND CLINICAL USE

Vivaglobin® , Immune Globulin Subcutaneous (Human), is indicated for the treatment of adult and pediatric patients with primary immune deficiency (PID) who require immune globulin replacement therapy.

Geriatrics (>65 years of age):
No specific studies in elderly patients have been conducted.

Pediatrics (2-16 years of age): See WARNINGS AND PRECAUTIONS, Pediatrics (2 – 16 years of age).

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, in persons with IgA deficiency who have known antibody against IgA and in patients who are hypersensitive to this drug or to any ingredient in the formulation or component of the container.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

- Products made from human plasma may contain infectious agents such as viruses, and theoretically, the Creutzfeldt-Jacob (CJD) agent (see General subsection, and PHARMACEUTICAL INFORMATION: Viral Inactivation)
- Immune Globulin (human) products have been reported to be associated with the following events:
  - aseptic meningitis syndrome
  - thrombo-embolism
  - renal impairment
  - hemolysis/hemolytic anemia
  - TRALI

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.

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®.

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 diseases. 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 **PART II: SCIENTIFIC INFORMATION, PHARMACEUTICAL INFORMATION** 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 inactivation by pasteurization (heat treatment of the aqueous solution at 60°C for 10 hours) and 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 thought by a physician to have been possibly transmitted by this product should be reported by the physician or other healthcare professional to CSL Behring at 1-613-783-1892. The physician should discuss the risks and benefits of this product with the patient.

During clinical trials, no cases of hepatitis A, B, C virus or HIV infections were reported with the use of Vivaglobin®

Special Populations

Pregnant Women: 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 only be used in pregnant women when the benefits outweigh the risks associated with its use.

Nursing Women: Vivaglobin® should only be used in nursing woman when the benefits outweigh the risks associated with its use.

Pediatrics (2 - 16 years of age): Vivaglobin® was evaluated in 6 children and 4 adolescents in the US and Canada study and in 16 children and 6 adolescents in the European 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® have not been studied in pediatric subjects under two years of age.

Geriatrics: Clinical studies 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.

Monitoring and Laboratory Tests

After injection of immunoglobulins, the transitory rise of the various passively transferred antibodies in the patient's blood may yield misleading positive serological testing results such as positive direct or indirect anti-globulin (Coomb's test) and anti-HBs/anti-HBc results in absence of viral transmission.

Periodic monitoring of renal function and urine output is particularly important in patients judged to have a potential increased risk for developing acute renal failure. Renal function, including measurements of blood urea nitrogen (BUN)/serum creatinine, should be assessed prior to initial infusion of Vivaglobin® and again at appropriate intervals thereafter.

If signs or symptoms of hemolysis are present after Vivaglobin® infusion, appropriate confirmatory laboratory testing, such as unconjugated serum bilirubin, serum haptoglobulin, Direct Antiglobulin Test (DAT) and serum LDH, should be done.

ADVERSE REACTIONS

Adverse Drug Reaction Overview with Post-Marketing Data:

Immunoglobulins as a class of products manufactured by CSL Behring have been widely used clinically, by the Intramuscular (i.m.) route, starting in the early 1950s. The Subcutaneous (s.c.) use of CE 1200 in the treatment of antibody deficiency syndromes has been approved in Europe, starting in 1994. Post-marketing surveillance of product administered i.m. or s.c., showed that the Immunoglobulins are well tolerated. The following undesirable effects have been reported in rare cases:

- allergic reactions including a fall in blood pressure, dyspnea, cutaneoous reactions, and in isolated cases reaching as far as anaphylactic shock, even when the patients have shown no hypersensitivity to previous administration.
- generalized reactions such as chills, fever, headache (headaches may also be caused by increased blood pressure), malaise, nausea, vomiting, arthralgia and moderate back pain.
- cardiovascular reactions, particularly if the product is inadvertently infused intravascularly.
- local reactions at the injection or infusion site: swelling, soreness, redness, induration, local heat, itching, bruising or rash.
- nervous system disorders – migraine, aseptic meningitis

Clinical Trial Adverse Drug 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 anaphylactic reaction (see **CONTRAINDICATIONS and WARNINGS AND PRECAUTIONS**). Because clinical trials are conducted under very specific conditions, the adverse drug reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug related adverse events and for approximating rate. 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 two clinical studies, Vivaglobin® was evaluated in 125 patients diagnosed with PID. The most frequent adverse reaction was local reaction at the injection site. Table 1 summarizes the most frequent adverse events by subject reported in the two clinical studies, and Table 2 summarizes the most frequent adverse events by infusion.

Table 1: Most Frequent Adverse Events by Subject* *Irrespective* of Causality

	US/Canada Clinical Study (65 subjects)	**Europe/Brazil Clinical Study (60 subjects)**
Adverse Events	No. of Subjects (% of total)	No. of Subjects (% of total)
Adverse Events at the Injection Site:	60 (92%)	44 (73%)
Non-Injection Site Reactions:		
Headache	31 (48%)	21 (35%)
Gastrointestinal disorder	24 (37%)	26 (43%)
Fever	16 (25%)	25 (42%)
Nausea	12 (18%)	0 (0%)
Sore throat	11 (17%)	5 (8%)
Rash	11 (17%)	2 (3%)
Allergic reaction	7 (11%)	5 (8%)
Skin disorder	5 (8%)	8 (13%)
Pain	6 (9%)	1 (2%)
Diarrhea	6 (9%)	1 (2%)
Cough increased	6 (9%)	1 (2%)

*Excluding infections

Table 2: Most Frequent Adverse Events by Infusion* *Irrespective* of Causality

	US/Canada Clinical Study (3656 infusions)	**Europe/Brazil Clinical Study (2297 infusions)**	**Both Studies (5953 infusions)**
Adverse Events (≥ 1% of infusions)	No. of AEs (Rate**)	No. of AEs (Rate**)	No. of AEs (Rate**)
Adverse Events at the Injection Site:	1789 (49%)	641 (28%)	2430 (41%)
Mild	1112 (30%)	626 (27%)	1738 (29%)
Moderate	601 (16%)	14 (1%)	615 (10%)
Severe	65 (2%)	0	65 (1%)
Unknown Severity	11 (< 1%)	1 (< 1%)	12 (< 1%)
Non-Injection Site Reactions:			
Headache	159 (4%)	49 (2%)	208 (3%)
Gastrointestinal disorder	36 (1%)	46 (2%)	82 (1%)
Fever	28 (1%)	78 (3%)	106 (2%)

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

Table 3 summarizes the most frequent related adverse events by subject reported in the two clinical studies, and Table 4 summarizes the most frequent related adverse events by infusion.

Table 3: Most Frequent Related Adverse Events by Subject*

	US/Canada Clinical Study (65 subjects)	**Europe/Brazil Clinical Study (60 subjects)**
Related Adverse Event (≥ 2 subjects in at least one study)	No. of Subjects (% of total)	No. of Subjects (% of total)
Adverse Events at the Injection Site:	60 (92%)	44 (73%)
Non-Injection Site Reactions:		
Headache	21 (32%)	0
Fever	2 (3%)	7 (12%)
Nausea	7 (11%)	0
Rash	4 (6%)	1 (2%)
Skin disorder	2 (3%)	2 (3%)
Asthenia	3 (5%)	0
Gastrointestinal disorder	3 (5%)	0
Tachycardia	2 (3%)	0
Urine abnormality	2 (3%)	0

*Excluding infections

Table 4: Most Frequent Related Adverse Events by Infusion*

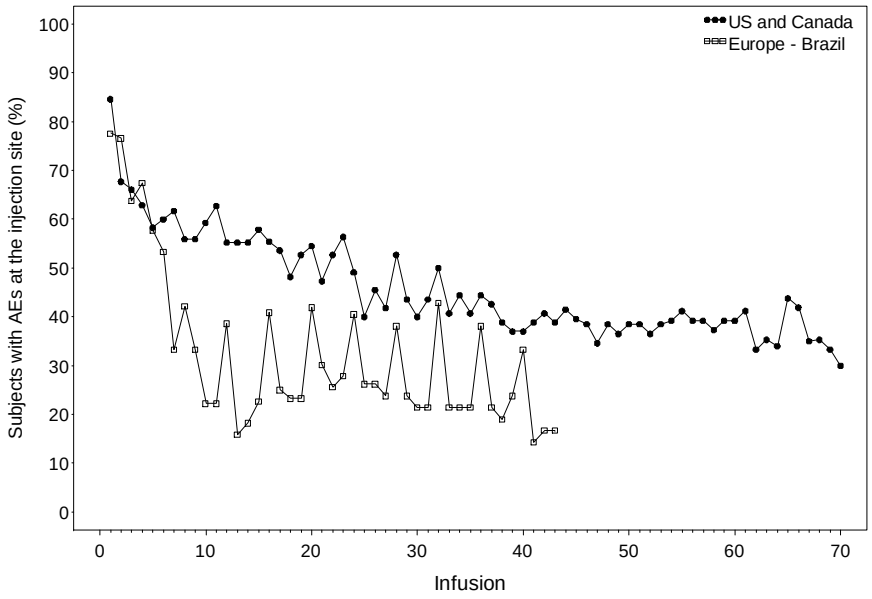
	US/Canada Clinical Study (3656 infusions)	**Europe/Brazil Clinical Study (2297 infusions)**	**Both Studies (5953 infusions)**
Related Adverse Event (≥ 2 AEs in at least one study)	No. of AEs (Rate**)	No. of AEs (Rate**)	No. of AEs (Rate**)
Adverse Events at the Injection Site:	1787 (49%)	633 (28%)	2420 (41%)
Non-Injection Site Reactions:			
Headache	59 (1.6%)	0	59 (1%)
Fever	2 (0.1%)	18 (0.8%)	20 (0.3%)
Rash	9 (0.2%)	2 (0.1%)	11 (0.2%)
Nausea	9 (0.2%)	0	9 (0.2%)
Skin disorder	3 (0.1%)	3 (0.1%)	6 (0.1%)
Nervousness	4 (0.1%)	0	4 (0.1%)
Asthenia	3 (0.1%)	0	3 (0.1%)
Chills	1 (< 0.1%)	2 (0.1%)	3 (0.1%)
Gastrointestinal disorder	3 (0.1%)	0	3 (0.1%)
Syncope	1 (< 0.1%)	2 (0.1%)	3 (0.1%)
Urine abnormality	3 (0.1%)	0	3 (0.1%)
Dyspnea	2 (0.1%)	0	2 (< 0.1%)
Gastrointestinal pain	2 (0.1%)	0	2 (< 0.1%)
Tachycardia	2 (0.1%)	0	2 (< 0.1%)

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

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®. Furthermore, the majority of injection site reactions resolved within four days. No serious local site reactions were observed. Four subjects discontinued Immune Globulin Subcutaneous (IGSC) therapy due to local site reactions.

Additionally, the number of subjects reporting local injection site reactions decreased substantially after repeated use (see Figure 1).

Figure 1: Subjects Reporting Local Site Reactions By Infusion



Note: Analysis is confined to 70 infusions.

Abnormal Hematologic and Clinical Chemistry Findings

No clinically significantly abnormal hematologic or clinical chemistry findings were observed in the clinical studies.

Small fluctuations of the safety laboratory results are commonly observed in routine safety laboratory testing, irrespectively of departures from the normal range values. To overcome the interpretation of natural variations within small study populations, a pre-defined changes analyses from baseline values was conducted using the following validated pre-defined changes parameters for the respective analytes:

Table 5: Summary of Pre-Defined Changes for Selected Laboratory Parameters Study CE1200_3001

Parameter	Pre-defined change (PC)	N*	No. (%) of subjects with PC
Hemoglobin	Decrease ≥ 1.2 mmol/L	62	3 (5%)
Hematocrit	Decrease ≥ 0.07	62	2 (3%)
Red blood cells	Decrease ≥$0.7*10^{12}$/L	62	4 (6%)
Platelet count	Decrease ≥ $93*10^{9}$/L	62	6 (10%)
Potassium	Decrease ≥ 1.1 mmol/L	64	1 (2%)
Glucose	Increase ≥ 4.2 mmol/L	64	3 (5%)

* N = Number of subjects with values at baseline and post-baseline

DRUG INTERACTIONS

Overview

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

Vivaglobin® should not be mixed with other medicinal products.

Drug-Drug Interactions

Please refer to **Overview.**

Drug-Food Interactions

Interaction with food has not been established.

Drug-Herb Interactions

Interaction with herbal products has not been established.

Drug-Laboratory Interactions

See WARNING AND PRECAUTIONS under Monitoring and Laboratory Tests.

DOSAGE 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.

Recommended Dose and Dosage Adjustment

All subjects who received Vivaglobin® in the clinical trials had previously been treated with immune globulin. It is recommended that the patient starts 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.

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 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 *(Roifman CM and al. 1987)*.

Table 6 shows the resulting serum trough IgG levels after Vivaglobin® treatment in the two clinical studies, which can be used as a dosing guide. Vivaglobin® administered at mean doses of 136% in the United States and Canada clinical study (158 mg/kg) and 101% in the European and Brazil clinical study (89 mg/kg) of the subject's immune globulin resulted in a mean increase in serum IgG levels of 255 and 86 mg/dL, respectively, over previous immune globulin-derived serum IgG trough levels before starting Vivaglobin® therapy.

Table 6: Weekly Vivaglobin® Doses And Resulting Serum IgG Trough Levels Compared With Previous Immune Globulin Therapy In Two Clinical Studies

Clinical Studies (number of subjects)	Mean IGSC Dose (mg/kg b.w.)	Mean IGSC Dose (as % of previous IgG dose)	Mean (range) Serum IgG Trough Levels (mg/dL IgG)	Mean Increase Over Baseline Serum IgG Trough Levels* (mg/dL IgG)
US/Canada (n = 51)	158	136	1040 (568 to 1810)	255
Europe/Brazil (n = 47)	89	101	922 (650 to 1684)	86

* Over previous immune globulin-derived serum IgG trough levels before starting Vivaglobin® therapy.

Serum IgG levels can be sampled at any time during routine weekly treatment. Subjects on IGSC therapy maintained relatively constant IgG levels, rather than the peak and trough pattern observed with monthly IGIV therapy.

Missed Dose

A missed dose should be administered as soon as possible to ensure an adequate IgG serum level.

Administration

DO NOT INJECT INTRAVENOUSLY.

In clinical studies 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 simultaneously into several sites using an infusion pump with a splitter to enable multiple simultaneous injections (CADD-Legacy® pumps were used in the study conducted in the U.S. 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.

Prior to use, allow the solution to reach ambient room temperature. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit. Do not use if the solution is cloudy or has particulates. The color of Vivaglobin® can vary from colorless to light brown.

1. Use aseptic technique when preparing and administering Vivaglobin® for injection.
2. Remove the cap from the vial to expose the central portion of the rubber stopper.

3. Wipe the rubber stopper of the vial with antiseptic solution and allow to dry.
4. DO NOT SHAKE. Withdraw the appropriate amount of Vivaglobin® by injecting air into the vial and withdraw the appropriate volume. Follow the manufacturer's instructions for preparing the pump and tubing.
5. Select the number of injection sites depending on the volume of the total dose.
6. Cleanse the injection site(s) with antiseptic solution followed by povidone-iodine using a circular motion from the inside to the outside of the injection site. The injection site should be clean, dry, and at least two inches away from other injection sites.
7. Vivaglobin® must not be infused into a blood vessel. To make sure that no blood vessel has been entered, slightly pull back the plunger of the syringe. If a blood vessel has been accidentally entered, this will be evident by blood flowing into the tubing of the catheter. An alternative injection site must then be chosen.
8. Inject Vivaglobin® following the manufacturer's instructions for using the infusion pump.
9. After administration, any unused solution and administration equipment should be discarded 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.

Reconstitution

Not applicable. Vivaglobin® is a ready to use solution of human immunoglobulin for subcutaneous infusion.

OVERDOSAGE

Consequences of an overdose are not known.

ACTION AND CLINICAL PHARMACOLOGY

Pharmacodynamics/ Mechanism of Action

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

Pharmacokinetics

Vivaglobin® is to be administered by injection into the subcutaneous tissue. Subcutaneous administration of immune globulin decreases bioavailability compared to intravenous administration (Smith and al.1972). The bioavailability of Vivaglobin® is approximately 73% compared to IGIV. Various factors, such as the site of administration and IgG catabolism, can affect absorption (Smith and al.1972, Waniewski and al.1993). With Vivaglobin® administration, peak serum IgG levels are lower than those achieved with immune globulin intravenous (IGIV). Subcutaneous administration results in relatively stable steady-state serum IgG levels when administered on a weekly basis (Waniewski and al.1993, Data on file). This serum IgG profile is representative of that seen in a normal population.

The pharmacokinetics (PK) of Vivaglobin® were 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 TRIALS). 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 7 summarizes additional pharmacokinetic parameters for this study including dosing and serum IgG peak and trough levels following treatment with IGIV and Vivaglobin®.

Table 7: Summary of Additional Pharmacokinetics Parameters – US and Canada PK Sub-study – Per-protocol Subjects

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

* For IGIV: weekly-equivalent dose

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. Table 8 summarizes additional PK parameters including Cmax, tmax, AUC, and clearance for Vivaglobin® from a supplementary analysis.

Table 8: Summary of Additional Pharmacokinetics Parameters – European and Brazilian PK Sub-study – Per-protocol Subjects

	Vivaglobin®
Number of Subjects	41
Dose Mean Range	 96 mg/kg 51 – 147 mg/kg
IgG trough levels Mean Range	 871 mg/dL 604 – 1401 mg/dL
Cmax Mean Range	 949 mg/dL 637-1517 mg/dL
tmax Mean Range	 2.46 d 0 – 6.95 d
AUC_{last} Mean Range	 62.25 g/L*d 39.91 – 102.24 g/L*d
*CLss/F: Mean Range	 1.54 mL/d/kg 0.83-2.60 mL/d/kg

*These results are based on 32 subjects only.

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.

Duration of Effect

In two studies (one was conducted in North America and the other in Europe and Brazil), subcutaneous weekly treatment with Vivaglobin® at doses between 50 and 200mg/kg b.w. resulted in stable IgG trough levels between 900 and 1000mg/dL at steady state (after 4 month of treatment) without major variations.

STORAGE AND STABILITY

Store Vivaglobin in the refrigerator at +2°C to +8°C. Vivaglobin may be stored at room-temperature (not to exceed +25°C) for up to 5 months within an overall storage period of 36 months at +2°C to +8°C. If the product is stored outside the refrigerator, please add the date removed from refrigeration and note a new expiry date on the carton on the space provided. The new expiry date should be 5 months from the date the product is removed from the refrigerator, or the previously stamped expiry date, whichever is shorter. Once the product is removed from refrigeration, it cannot be returned to the refrigerator.

Immune Globulin Subcutaneous (Human), Vivaglobin®, is stable for the period indicated by the expiration date on its label. Do not freeze. Keep vials in their storage box until use.

Since the product contains no antimicrobial preservative, do not begin administration more than 4 hours after the vial has been opened. Destroy unused portions to prevent the possibility of subsequent use of a solution that may have become contaminated.

SPECIAL HANDLING INSTRUCTIONS

Vivaglobin®, Immune Globulin Subcutaneous (Human), is a ready-for-use solution and should be administered at room temperature.
Vivaglobin® is a clear solution. The color can vary from colorless to pale-yellow up to light-brown during shelf-life. Do not use solutions that are cloudy or contain residues (deposits/particles).

Any unused product (solution) should be disposed of in accordance with local authorities' requirements.

DOSAGE FORMS, COMPOSITION AND PACKAGING

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

Single 3 mL vial
Box of ten 3 mL vials
Single 10 mL vial
Box of two 10 mL vials
Box of ten 10 mL vials
Box of twenty 10 mL vials
Single 20 mL vial
Box of ten 20 mL vials
Box of twenty 20 mL vials

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Proper name: Immune Globulin Subcutaneous (Human)

Chemical name: Immune Globulin Subcutaneous (Human)

Molecular formula and molecular mass: Not applicable.

Molecular Size Distribution:

Polymers + Fragments	≤ 10%
Monomers + Dimers	≥ 90%

Structural formula:

The active biological component of the drug substance is human polyvalent immunoglobulin G (IgG) isolated from human plasma. The Y-shaped molecule consists of two identical heavy chains (H-chains) of about 420 amino acid residues and two identical light chains (L-chains) of about 210 amino acid residues. The H-chain is composed of four distinct areas or domains (V_H, C_H1 – C_H3) whereas the L-chain comprises two domains (V_L and C_L). V_H and V_L show considerable sequence variation whereas the other domains of the H-chain (C_H1 – C_H3) as well as of the C_L are constant. H-chains are linked together and to the L-chain by inter-chain disulfide bonds and noncovalent interactions. IgG is defined by comprising H-chains of the γ-type. L-chains may belong either to the κ- or the λ-type. Molecular weights are about 50 kDa for the H-chain, about 25 kDa for the L-chain and about 150 kDa for the entire IgG-molecule. The structural combination of V_H and V_L domains determines the shape of the antigen binding site or paratope. Hence, IgG has two identical paratopes, situated at the N-terminal end of the molecule. Together, the two C-terminal domains of both H-chains (C_H2 and C_H3) form the Fc-part of the IgG-molecule, which is responsible for several effector activities of the IgG-molecule. About 3% of the molecular mass is carbohydrates linked to C_H2 located in the Fc-part of the molecule. Human IgG has four subclasses, namely IgG1, IgG2, IgG3 and IgG4, which differ in the amino acid composition of the γ -chains, their relative concentration, numbers and position of inter-chain disulfide bonds and biological activities.

Physicochemical properties:

Electrophoretic Mobility:

Gammaglobulin	≥ 96% (Cellulose Acetate Strip Electrophoresis)
IgG	≥ 95% of Ig (Nephelometry)

IgG-subclass distribution:

IgG_1	57 – 73%
IgG_2	20 – 32%
IgG_3	3 – 5%
IgG_4	3 – 6%

Biological Activity:

The drug substance (polyvalent ultraconcentrate) contains the normal antibody spectrum of the donor population (see the section below concerning Hepatitis A virus antibody activity). Antiviral and antibacterial potencies are at least tenfold increased by the manufacturing process in comparison to the initial pooled human plasma for fractionation.

Product Characteristics

Vivaglobin®, Immune Globulin Subcutaneous (Human), is supplied as a sterile liquid to be administered by the subcutaneous route. It 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 U.S. Food and Drug Administration-licensed serological assays for hepatitis B surface antigen and antibodies to hepatitis C virus (HCV) and human immunodeficiency virus type 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).

Viral Inactivation

The manufacturing procedure of 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 removal by partitioning (precipitation) and inactivation by pasteurization in aqueous solution at 60°C for 10 hours. Total mean cumulative virus reductions ranged from 4.8 to ≥ 11.6$\log_{10}$ as shown in Table 9.

Table 9: Mean Virus Reduction Factors [log_{10}] for Vivaglobin

Virus Studied	Virus Removal by Partitioning	Virus Inactivation by Pasteurisation	Mean Overall Virus Reduction Factor
Enveloped viruses			
HIV	≥ 3.1	≥ 6.5	≥ 9.6
BVDV	≥ 1.5	≥ 8.7	≥ 10.2
PRV	≥ 3.7	≥ 7.9	≥ 11.6
WNV	-	≥ 9.3	≥ 9.3
Non-enveloped viruses			
Picarnoviruses[1] (model virus for HAV)	≥ 3.4	3.7[2]	≥ 7.1
Parvovirus[3] (model virus for B19V)	≥ 2.5	2.3	≥ 4.8
B19V	-	≥ 5.0	≥ 5.0

[1] Removal was studied employing BEV (bovine enterovirus) and inactivation was studied employing PEV (porcine enterovirus)

[2] Inactivation of HAV by pasteurisation (in porcine immunoglobulin to avoid neutralization of HAV by human IgG) ≥ 5.7 log_{10}

[3] Removal was studied employing MVM (minute virus of mice) and inactivation was studied employing CPV (canine parvovirus).

Additionally, the manufacturing process was investigated for its capacity to decrease the levels of purified prion protein, an experimental agent of transmissible spongiform encephalopathy (TSE), considered as a model for the variant Creutzfeldt-Jakob disease (vCJD) and Creutzfeldt-Jakob disease (CJD) agents. Several of the individual production steps in the Vivaglobin® manufacturing process have been shown to decrease purified prion protein, leading to an overall reduction of at least 5 log_{10}. These studies provide reasonable assurance that low levels of vCJD/CJD agent infectivity, if present in the starting material, would be removed.

CLINICAL TRIALS

Two open-label, prospective, multicenter, multinational clinical studies evaluated the pharmacokinetics, efficacy, safety and tolerability of Vivaglobin®, Immune Globulin Subcutaneous (Human), in adult and pediatric subjects with primary immune deficiency (PID). Both studies yielded similar efficacy and safety results.

Study demographics and trial design are presented in Table 10.

Table 10: Summary of patient demographics for clinical trials in specific indication

Study #	Trial design	Dosage, route of administration and duration	Study subjects (N = number)	Mean age (Range)	Gender
Study CE1200_3001 19 centers -United States (16) -Canada (3)	Open-label, prospective, Phase 2/3, multicenter trial	Average starting dose of CE1200: 120% of the weekly-equivalent IGIV dose Dose of CE1200 was then adjusted to 137% of the weekly equivalent IGIV dose One SC infusion per week	N = 65	35 years (5 - 66 years)	37 M 28 F
Study CE1200_3002 12 centers -Germany (4) -Poland (2) -Spain (3) -Sweden (1) -Austria (1) -Brazil (1)	Open-label, prospective Phase 3, multinational trial	CE1200 dose equal to the weekly-equivalent of the previous Ig replacement therapy One SC infusion per week	N = 60	21 years (3 - 74 years)	43 M 17 F

In a study conducted in the United States and Canada, 65 adult and pediatric PID subjects previously treated monthly with Immune Globulin Intravenous (Human) (IGIV) were switched to weekly subcutaneous administrations of Vivaglobin® for 12 months. The pharmacokinetic phase of this study established the Vivaglobin® dose that provided an IgG systemic exposure (area under the curve; AUC) that was not inferior to the AUC of the weekly-equivalent IGIV dose. 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. This provided a mean serum IgG trough level of 1040 mg/dL, which is a mean increase of 255 mg/dL over previous immune globulin-derived serum IgG trough levels before starting Vivaglobin® therapy.

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) IgG_1: 703 mg/dL, IgG_2: 278 mg/dL, IgG_3: 36 mg/dL, IgG_4: 30 mg/dL.

In the other 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 6 months. Forty-nine subjects had been on IGIV and 11 subjects had been on another brand of Immune Globulin Subcutaneous (Human) (IGSC) replacement therapy before entering the study. The per-protocol efficacy analysis included 47 subjects. 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. This provided a mean serum IgG level of 922 mg/dL, which is a mean increase of 86 mg/dL over previous immune globulin-derived serum IgG trough levels before starting Vivaglobin® therapy.

In this study, the annualized rate of serious bacterial infections in the efficacy phase was 0.04 infections per subject per year (one-sided upper 99% confidence interval: 0.21). Pneumonia was reported in one subject. The annualized rate of any infections was 4.3 infections per subject per year.

Table 11 summarizes the dosing, efficacy, and serum IgG trough levels for the two clinical studies. In contrast to serum IgG levels observed with monthly IGIV treatment (rapid peak followed by a slow decline), the IgG levels obtained under weekly subcutaneous therapy exhibited stable levels.

Table 11: Dosage, Annualized Rate of Serious Bacterial Infections and Serum IgG Trough Levels Following Treatment with Vivaglobin® - Per-protocol Subjects Efficacy Phase

	US/Canada Clinical Study (12 months)	**Europe/Brazil Clinical Study (6 months)**
Number of Subjects	51	47
Vivaglobin® Dose: **Mean % Previous Immune Globulin Dose (range):**	136% (99 – 188%)	101% (81 – 146%)
Mean	158 mg/kg b.w.	89 mg/kg b.w.
Range	34 – 352 mg/kg b.w.	51 – 147 mg/kg b.w.
Annual/Annualized Rate of Serious Bacterial Infections	0.04 infections/subject year	0.04 infections/subject year
Annual/Annualized Rate of Any Infections	4.4 infections /subject year	4.3 infections/subject year
Serum IgG Trough Levels:		
Mean	1040 mg/dL	922 mg/dL
Range	568 – 1810 mg/dL	650 – 1684 mg/dL
Mean Increase Over Baseline Serum IgG Trough Levels*	255 mg/dL	86 mg/dL

b.w. – body weight

* Over previous immune globulin-derived serum IgG trough levels before starting Vivaglobin® therapy.

Table 12 provides a summary of missed school or work and hospitalization due to infection, which were secondary endpoints for both studies.

Table 12: Summary of Secondary Efficacy Variables (Per-protocol set) – Efficacy Phase

	US/Canada Clinical Study (12 months)	**Europe/Brazil Clinical Study (6 months)**
Number of Subjects	51	47
Total Number of Subject Days	18,949	9,278
Total Number of Days Missed School/Work Due to Infection (%)	192 (1.0%)	69 (0.7%)*
Annual Rate Missed School/ Work Due to Infection (days/ subject year)	3.70	2.77*
Total Number of Days Hospitalized Due to Infection (%)	12 (< 0.1%)	12 (0.1%)
Annual Rate of Hospitalization (days/subject year)	0.23	0.47

*Excluding one subject who missed 191 out of 196 workdays in the efficacy phase due to intense general fatigue not related to any specific infection.

DETAILED PHARMACOLOGY

Please refer to ACTION AND CLINICAL PHARMACOLOGY section.

MICROBIOLOGY

Not applicable.

TOXICOLOGY

Safety Pharmacology in dogs: At a dose of 400 mg/kg b.w. (s.c.) and up to 480 mg/kg b.w. intramuscular (i.m.), no relevant adverse effects were observed when cardiovascular, respiratory, hematological parameters, and clinical chemistry were evaluated.

Acute toxicity i.m. studies in mice and rats: The highest dose tested was 8 g/kg (50 mL/kg) b.w. for mice (representing the technical limit) and 1.6 g/kg (10 mL/kg) b.w. for rats. The product was well tolerated at all doses tested. No adverse clinical signs were observed and no deaths occurred.

Acute toxicity s.c. studies in mice and rats: No adverse reaction was observed following a dose of 600 mg/kg b.w.

Local tolerance i.m. or s.c. in rabbits: Clinical, pathological, and histopathological examinations revealed no relevant alternations following a dose of 80 mg / rabbit. Local tolerance was good.

Preclinical Toxicity: Well tolerated at doses representing a multiple of the dose used in humans (up to approximately 80-fold when compared to a human dose), whether injected intramuscularly or subcutaneously.

Neoantigenicity:

- **Evaluation in rabbits (9 x 50 mg/rabbit over 18 days):** Rabbit sera tested by Ouchterlony confirmed no formation of neoantigens as a result of the pasteurization step.

- **Passive cutaneous anaphylaxis (PCA) test in guinea pigs:** Test animals were injected (i.v.) with adsorbed (to unpasteurized preparation) rabbit antisera (antisera to pasteurized product) followed by intracutaneous injection of the pasteurized and unpasteurized product (contralateral flank). PCA confirmed no formation of neoantigens as a result of the pasteurization step.

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PART III: CONSUMER INFORMATION

Vivaglobin®
Immune Globulin Subcutaneous (Human)

This leaflet is part III of a three-part "Product Monograph" published when Vivaglobin® was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything 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. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:

Vivaglobin® is a medication used to treat adults and children who need antibody replacement therapy due to primary immune deficiency.

Vivaglobin® is supplied as a sterile liquid in single-use vials and is given by injection 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 dose and treatment schedule for Vivaglobin®.

What it does:

Vivaglobin® treats primary immune deficiency, 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 (germs). However, when our immune system is not working properly, it is unable to produce these valuable antibodies, leaving us more vulnerable to 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 these infection-fighting proteins. By replacing these important antibodies, Vivaglobin® helps make people with primary immune deficiency better able to avoid infections and fight them when they do occur.

When it should not be used:

People who have a history of severe allergic reactions to immunoglobulin treatment 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 the medicinal ingredient is:

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 disease and illness.

What the important nonmedicinal ingredients are:

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

For a full listing of nonmedicinal ingredients see Part 1 of the product monograph.

What dosage forms it comes in:

Vivaglobin® is a solution for subcutaneous infusion.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

- Products made from human plasma may contain infectious agents such as viruses, and theoretically, the Creutzfeldt-Jacob (CJD) agent.
- Immune Globulin (human) products have been reported to be associated with the following events:
  - aseptic meningitis syndrome
  - thrombo-embolism
  - renal impairment or dysfunction
  - anemia (hemolysis, hemolytic)
  - transfusion-related acute lung injury (TRALI)

BEFORE you use Vivaglobin® talk to your doctor or pharmacist if:

- you are pregnant or think that you may be pregnant;
- you are nursing;
- you have a history of allergic or other adverse reactions to immune globulins;
- you recently have been vaccinated.
- you have been previously advised that you have IgA deficiency.

INTERACTIONS WITH THIS MEDICATION

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.

PROPER USE OF THIS MEDICATION

How do I use Vivaglobin®?

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

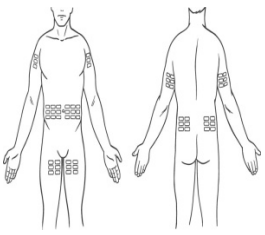
Your doctor will determine the appropriate dose for your treatment.

Your doctor or healthcare professional 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 injection of Vivaglobin®:

- Abdomen
- Thighs
- Upper arms
- Hip



For proper selection of injection site, please consult your doctor or healthcare professional.

Instructions for administration

The following instructions are intended only as a guide. Before administering Vivaglobin®, you should be under the care of a doctor and should have received proper training on preparation and administration from a healthcare professional.

1. Prior to use, allow the vial(s) of Vivaglobin® to reach room temperature, +20°C to +25°C. On a clean, smooth, flat surface, such as a table, assemble all the supplies you will need for your treatment, such as your Vivaglobin® product vials, treatment diary or logbook, an infusion pump, administration tubing, subcutaneous injection sets, y-sites, alcohol wipes, antiseptic skin preps, syringe(s), needle(s), gauze or transparent dressing, tape and a sharps disposal container. Your doctor or healthcare professional can give you a complete list of supplies. Discuss with your doctor or healthcare professional whether you should use gloves when preparing and injecting Vivaglobin® (Fig. 1).


Fig. 1

2. There are several different types of ambulatory infusion pumps that may be used to administer Vivaglobin®. Your healthcare professional 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 healthcare professional.

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


Fig. 2

4. Be sure to visually inspect Vivaglobin® for particles in the solution and discoloration before administration by gently rotating the 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 tamper-evident cap is missing, do not use it. Check the expiry date on each vial of Vivaglobin®. Do not use beyond the expiry date. (Fig.3)


Fig. 3

5. Remove the cap from the vial to expose the central portion of the rubber stopper. Disinfect the rubber stopper with an alcohol wipe and allowing it to dry. While wiping the rubber stopper, be sure not to shake the Vivaglobin® vial. (Figs. 4 and 5)


Fig. 4


Fig. 5

6. Prepare the equipment used to withdraw Vivaglobin® from the vial. If you are using a syringe, using aseptic technique as instructed by your healthcare professional, attach a needle to the syringe tip. (Fig. 6)


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)


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. 8

9. Select an appropriate injection site(s), depending on the amount required for your total Vivaglobin® dose and the instructions of your healthcare professional. 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 professional recommends that you administer Vivaglobin® using multiple sites, ensure that each site is at least two inches apart. (The maximum recommended infusion volume per injection site is 15 mL). (Fig. 9)

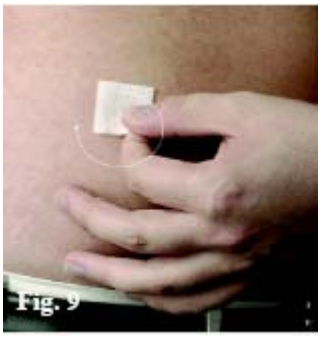


Fig. 9

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

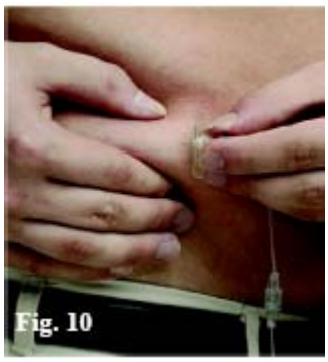


Fig. 10

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 injection site. (Fig. 11)

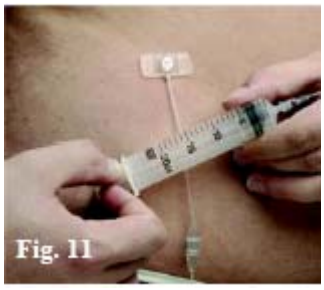


Fig. 11

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

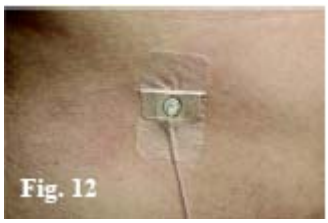


Fig. 12

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

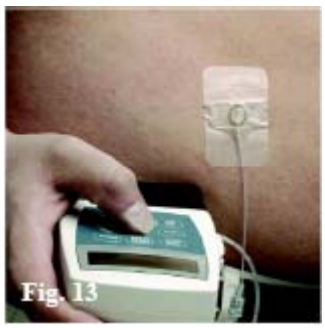


Fig. 13

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


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)


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 administering Vivaglobin®. If you have not received such training, please consult your doctor before attempting to administer Vivaglobin®. If you experience any problems or need more information regarding your subcutaneous treatment, contact your doctor or healthcare professional.

Usual dose:

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.

Overdose:

There is no overdose information for Vivaglobin®

Missed Dose:

Inform your doctor if you missed a dose. Your next dose should be administered as soon as possible to ensure an adequate protection.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

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, and tended to decrease substantially over time after several injections.

Please contact your healthcare professional if you would like more information on managing these reactions.

Other side effects may include:

- **Headache (Headaches due to high blood pressure)**
- **Gastrointestinal disorder**
- **Fever**
- **Nausea**
- **Sore throat**
- **Rash**
- **Allergic reaction**
- **Increased cough**
- **Pain**
- **Diarrhea**
- **Migraine**
- **Aseptic meningitis**

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

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
		Only if severe	In all cases	
Common	Mild injection site reactions	✓		
	Headache	✓		
Uncommon	Gastrointestinal disorder		✓	
	Fever		✓	
	Nausea		✓	
	Sore throat		✓	
	Rash		✓	
	Allergic reaction		✓	
	Skin disorder			
	Anaphylactic reaction			✓

As with any immunoglobulin preparation, there is a rare possibility that an anaphylactic reaction could occur. Prior to starting home treatment with Vivaglobin®, discuss this possibility with your doctor or pharmacist so that appropriate treatment of this reaction is available.

This is not a complete list of side effects. For any unexpected effects while taking Vivaglobin® *, contact your doctor or pharmacist.*

HOW TO STORE IT

Vivaglobin® is supplied in single-use vials. It contains no preservatives, so any unused portion should be discarded immediately after injection. Store Vivaglobin in the refrigerator at +2°C to +8°C. Vivaglobin may be stored at room-temperature (not to exceed +25°C) for up to 5 months within an overall storage period of 36 months at +2°C to +8°C. If the product is stored outside the refrigerator, please add the date removed from refrigeration and note a new expiry date on the carton on the space provided. The new expiry date should be 5 months from the date the product is removed from the refrigerator, or the previously stamped expiry date, whichever is shorter. Once the product is removed from refrigeration, it cannot be returned to the refrigerator.

Immune Globulin Subcutaneous (Human), Vivaglobin, is stable for the period indicated by the expiration date on its label. Do not freeze. Keep vials in their storage box until use.

Keep Vivaglobin® and all other medications out of the reach of children.

REPORTING SUSPECTED SIDE EFFECTS

To monitor drug safety, Health Canada collects information on serious and unexpected effects of drugs. If you suspect you have had a serious or unexpected reaction to this drug you may notify Health Canada by:

toll-free telephone: 866-234-2345
toll-free fax 866-678-6789
By email: cadrmp@hc-sc.gc.ca

By regular mail:
National AR Centre
Marketed Health Products Safety and Effectiveness Information Division
Marketed Health Products Directorate
Tunney's Pasture, AL 0701C
Ottawa ON K1A 0K9

NOTE: Before contacting Health Canada, you should contact your physician or pharmacist.

*** We recommend that CSL Behring Canada, Inc. be copied when reporting suspected side effects, at the following address:***

adversereporting@cslbehring.com

or be informed by pager
Pager Number: 1-613-783-1892

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals, can be found at:
http://www.cslbehring.ca

or for more information you may communicate with the sponsor, CSL Behring Canada, Inc. at: 1-613-783-1892

This leaflet was prepared by CSL Behring Canada, Inc.
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