HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use Vivaglobin safely and effectively. See full prescribing information for Vivaglobin.

Vivaglobin®
Immune Globulin Subcutaneous (Human)
16% Liquid
Initial U.S. Approval: 2006

----------RECENT MAJOR CHANGES----------

Dosage and Administration (2.3) 04/2010
Warnings and Precautions (5.1, 5.2, 5.3) 04/2010

----------INDICATIONS AND USAGE----------

Vivaglobin is an Immune Globulin Subcutaneous (Human) (IGSC), 16% Liquid indicated for the treatment of primary humoral immunodeficiency (PI) (1).

----------DOSAGE AND ADMINISTRATION----------

For subcutaneous infusion *only*. DO NOT INJECT INTO A BLOOD VESSEL.

Start patients on treatment with Vivaglobin 1 week after having received Immune Globulin Intravenous (Human) (IGIV) infusions at regular intervals for a period of at least 3 months.

Initial Weekly Dose (2.3)

The initial weekly dose of Vivaglobin is calculated to achieve a systemic serum IgG exposure (area under the concentration-time curve [AUC]) not inferior to the AUC of the previous IGIV treatment.

- Vivaglobin weekly dose (in grams [g]) = $\frac{\text{1.37 x previous IGIV dose (g)}}{\text{No. of weeks between IGIV doses}}$
- Divide by 0.16 to convert the dose in g to milliliters (mL).

Dose Adjustment (2.3, Table 1)

- Doses may need to be adjusted over time based on the patient's clinical response and serum immunoglobulin G (IgG) trough levels.
- To determine if a dose adjustment should be considered, measure the serum IgG trough level during IGIV therapy prior to switching to Vivaglobin and again after 2 to 3 months of treatment with Vivaglobin. Adjust the Vivaglobin dose to achieve a serum IgG trough level that is equal to the last trough level during prior IGIV therapy plus 180 mg/dL.

Administration (2.4)

- Infuse subcutaneously, preferably in the abdomen, thigh, upper arm, and/or lateral hip.
- Divide doses >15 mL and infuse into multiple sites that are at least two inches apart.
  - Adults – Up to six simultaneous sites
  - Children <45 kg (99 pounds) – Up to three simultaneous sites
  - Patients ≥65 years – Up to four simultaneous sites

  If necessary, additional sites can be used consecutively during an infusion.
- Administer at a rate of ≤20 mL/hour per site. The maximum infusion rate should not exceed a total of 3 mg/kg/minute (1.13 mL/kg/hour) for all simultaneous infusion sites combined.
- Ensure that patients are not volume depleted.

----------DOSAGE FORMS AND STRENGTHS----------

16% IgG (160 mg/mL) for subcutaneous infusion (3)

----------CONTRAINDICATIONS ----------

- Anaphylactic or severe systemic reaction to Immune Globulin (Human) (4)
- IgA-deficient patients with antibodies against IgA or a history of hypersensitivity (4)

----------WARNINGS AND PRECAUTIONS----------

- IgA-deficient patients with antibodies against IgA are at greater risk of developing severe hypersensitivity and anaphylactic reactions. Discontinue use if a hypersensitivity reaction occurs. Epinephrine should be immediately available to treat any acute severe hypersensitivity reactions (5.1).
- Aseptic meningitis syndrome has been reported to occur infrequently with IGIV treatment and with Vivaglobin treatment (5.2).
- Monitor patients for reactions reported to occur with IGIV treatment that may occur with Vivaglobin, including renal dysfunction/failure, thrombotic events, hemolysis, and transfusion-related acute lung injury (TRALI) (5.3).
- Vivaglobin is made from human plasma and may contain infectious agents, e.g., viruses and, theoretically, the Creutzfeldt-Jakob disease (CJD) agent (5.4).

----------ADVERSE REACTIONS----------

The most common adverse reactions (observed in ≥5% of study subjects) were local injection-site reactions (swelling, redness, and itching), headache, nausea, rash, asthenia, and gastrointestinal disorder (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact the CSL Behring Pharmacovigilance Department at 1-866-915-6958 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch.*

----------DRUG INTERACTIONS----------

- The passive transfer of antibodies may interfere with the response to live virus vaccines (7.1).
- The passive transfer of antibodies may lead to misinterpretation of the results of serological testing (7.2).

----------USE IN SPECIFIC POPULATIONS----------

- Pregnancy: No human or animal data. Use only if clearly needed (8.1).

See 17 for PATIENT COUNSELING INFORMATION and the accompanying FDA-approved patient labeling.

Revised: April 2010

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CSL Behring

FULL PRESCRIBING INFORMATION

Vivaglobin®
Immune Globulin Subcutaneous (Human)
16% Liquid

1 INDICATIONS AND USAGE

Vivaglobin is an Immune Globulin Subcutaneous (Human) (IGSC), 16% Liquid indicated as replacement therapy for primary humoral immunodeficiency (PI). This includes, but is not limited to, the primary immunodeficiency in common variable immunodeficiency (CVID), X-linked agammaglobulinemia, congenital agammaglobulinemia, Wiskott-Aldrich syndrome, and severe combined immunodeficiencies.

2 DOSAGE AND ADMINISTRATION

For subcutaneous infusion *only*. DO NOT INJECT INTO A BLOOD VESSEL.

2.1 Self-Administration

Self-administration is appropriate for some patients. If self-administration is planned, the healthcare professional should provide the patient with instructions and training for subcutaneous infusion in the home or other appropriate setting (*see Patient Counseling Information [17.1] and the FDA-Approved Patient Labeling*).

2.2 Preparation and Handling

Vivaglobin is a colorless to light brown solution. Do not use if the solution is cloudy (turbid) or contains particulates.

- Prior to administration, bring the Vivaglobin vial(s) to room temperature. Then, visually inspect each vial for particulate matter by gently swirling the vial, and check for discoloration by holding it up to the light.
- Check the product expiration date on the vial label. Do not use beyond the expiration date.
- Do not mix Vivaglobin with other products.
- Do not shake the Vivaglobin vial.
- Use aseptic technique when preparing and administering Vivaglobin.
- The Vivaglobin vial is for single-use only. Discard all administration equipment and any unused product immediately after each infusion in accordance with local requirements.

2.3 Dosage

The dose should be individualized based on the patient's clinical response to Vivaglobin therapy and serum immunoglobulin (IgG) trough levels.

Begin treatment with Vivaglobin one week after the patient has received a regularly scheduled Immune Globulin Intravenous (Human) (IGIV) infusion. Prior to receiving treatment with Vivaglobin, patients need to have been receiving IGIV treatment for at least 3 months at dosing intervals of either every 3 weeks or every 4 weeks.

The initial weekly dose of Vivaglobin is established by converting the monthly IGIV dose into a weekly equivalent and increasing it using a dose adjustment factor (*see Initial Weekly Dose*). The goal is to achieve a systemic serum IgG exposure (area under the concentration-time curve [AUC]) not inferior to the AUC of the previous IGIV treatment (*see Pharmacokinetics [12.3]*).

Prior to switching treatment from IGIV to Vivaglobin, obtain the patient's serum IgG trough level to guide subsequent dose adjustment (*see Dose Adjustment*). After 2 to 3 months, weekly administration of Vivaglobin will lead to stable steady-state serum IgG levels with lower IgG peak levels and higher IgG trough levels compared with monthly IGIV treatment.

Initial Weekly Dose

To calculate the initial weekly dose of Vivaglobin, multiply the previous IGIV dose in grams (g) by the dose adjustment factor of 1.37, then divide this dose by the number of weeks between doses during the patient's previous IGIV treatment (i.e., 3 or 4).

$$\text{IGSC weekly dose (g)} = \frac{1.37 \times \text{previous IGIV dose (g)}}{\text{Number of weeks between IGIV doses}}$$

To convert the Vivaglobin dose (g) to milliliters (mL), divide the dose in grams (g) by 0.16.

Dose Adjustment

Over time, the dose may need to be adjusted to achieve the desired clinical response and serum IgG trough level. To determine if a dose adjustment should be considered, measure the patient's serum IgG trough level on IGIV prior to switching to Vivaglobin and every 2 to 3 months after switching from IGIV to Vivaglobin.

To achieve the same AUC with Vivaglobin as with the previous IGIV treatment, follow these steps:

1. Estimate the target serum IgG trough level on weekly Vivaglobin treatment, which is derived as follows:

Target concentration (mg/dL) during Vivaglobin treatment =
the last trough level during prior IGIV treatment + 180 mg/dL

2. In Table 1, find the additional Vivaglobin dose to be administered, based on the patient's body weight, and the difference between the target IgG concentration (mg/dL) and the observed trough level during Vivaglobin treatment.

Additional dosage increments may be indicated based on the patient's clinical response (infection frequency and severity).

Table 1: Adjustment (±mL) of the Weekly Vivaglobin Dose Based on the Difference (±mg/dL) From the Target Serum IgG Trough Level*

Difference From Target IgG Trough Level* (mg/dL)	Body Weight (kg)												
	10	15	20	30	40	50	60	70	80	90	100	110	120
	Dose Adjustment (mL per Week)†												
100	1	2	2	3	4	5	6	7	8	9	10	11	12
150	2	2	3	5	6	8	9	11	12	14	15	17	18
200	2	3	4	6	8	10	12	14	16	18	20	23	25
250	3	4	5	8	10	13	15	18	20	23	26	28	31
300	3	5	6	9	12	15	18	22	25	28	31	34	37
350	4	5	7	11	14	18	22	25	29	32	36	39	43
400	4	6	8	12	16	20	25	29	33	37	41	45	49
450	5	7	9	14	18	23	28	32	37	41	46	51	55
500	5	8	10	15	20	26	31	36	41	46	51	56	61

* Target IgG concentration (mg/dL) during Vivaglobin treatment equals the last observed trough level during prior IGIV treatment plus 180 mg/dL.

† Dose adjustment in mL is based on the slope of the serum IgG trough level response to Vivaglobin dose increments (6.1 mg/dL per increment of 1 mg/kg per week).

For example, if a patient with a body weight of 70 kg has an actual IgG trough level of 900 mg/dL and the target trough level is 1000 mg/dL, this results in a difference of 100 mg/dL. Therefore, increase the weekly dose of Vivaglobin by 7 mL.

Monitor the patient's clinical response, and repeat the dose adjustment process as needed.

2.4 Administration

Vivaglobin is for subcutaneous infusion *only*. DO NOT INJECT INTO A BLOOD VESSEL.

Vivaglobin is for subcutaneous infusion, preferably in the abdomen, thigh, upper arm, and/or lateral hip. Multiple injection sites should be at least two inches apart, and the actual point of injection should be changed with each weekly administration.

- Infusion volume – Do not exceed 15 mL per site. Divide doses greater than 15 mL and infuse into a maximum of three simultaneous sites for children weighing less than 45 kg (99 pounds), a maximum of six simultaneous sites for adults up to age 65, and a maximum of four simultaneous sites for patients 65 years of age and older. If necessary, additional sites can be used consecutively during an infusion.
- Infusion rate – The maximum recommended infusion rate is 20 mL per hour per site and should not exceed a total of 3.0 mg/kg/minute (1.13 mL/kg/hour) for all simultaneous injection sites combined.

Ensure that patients are not volume depleted.

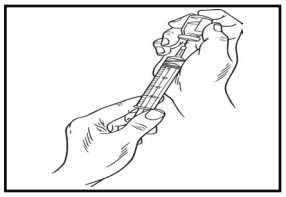
Follow the steps below and use aseptic technique to administer Vivaglobin. For information about subcutaneous infusion in the home or other appropriate setting, *see Patient Counseling Information (17.1)*.

1. Assemble supplies – Place the Vivaglobin vial(s) and all supplies needed for the infusion on a clean, flat surface.

2. Thoroughly wash and dry hands – The use of gloves when preparing and administering Vivaglobin is optional.

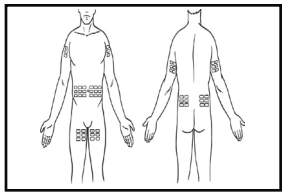
3. Clean the vial stopper – Remove the protective cap from the vial to expose the central portion of the rubber stopper. Clean the stopper with alcohol and allow it to dry.

4. Prepare and fill the syringe(s) – Using a sterile syringe and needle, pull back on the plunger to draw air into the syringe that is equal to the amount of Vivaglobin to be withdrawn. Then, insert the needle into the vial stopper and inject the air into the vial. Finally, withdraw the desired volume of Vivaglobin. If multiple vials are required to achieve the desired dose, repeat this step with another syringe.



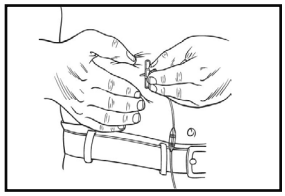
5. Fill and prime the infusion pump – Follow the manufacturer's instructions for filling the pump reservoir and for preparing the pump, administration tubing, and Y-site connection tubing, if needed. Be sure to prime the administration tubing to ensure that no air is left in the tubing or needle by filling the tubing/needle with Vivaglobin.

6. Select the injection site(s) – The number and location of injection sites depends on the volume of the total dose. Doses greater than 15 mL should be divided and infused into multiple sites that are at least two inches apart. The recommended number of simultaneous injection sites is up to six for adults, up to three for children who weigh less than 45 kg (99 pounds) and up to four for patients ages 65 and over. If necessary, additional injection sites can be used consecutively.



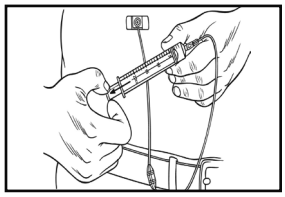
7. Clean the injection site(s) – Using an antiseptic solution, clean each site beginning at the center and working outward in a circular motion. Allow each site to dry before proceeding.

8. Insert the needle – Based on the patient's body mass, grasp or spread the skin; then insert the needle into the subcutaneous tissue.



9. Check for proper placement of the needle. Vivaglobin must not be injected into a blood vessel – After inserting each needle into the subcutaneous tissue and before starting the infusion, test to make sure that a blood vessel has not been accessed accidentally. To do this, attach a sterile syringe to the end of the primed administration tubing, gently pull back on the plunger, and see if any blood is flowing back into the tubing. If blood is present, remove and discard the needle and administration tubing. Repeat steps 5 and 8 (priming and needle insertion) using a new needle, new administration tubing, and a different injection site.

10. Secure the needle to the skin – Apply sterile gauze or transparent dressing over each site to hold the needle in place. If using multiple, simultaneous injection sites, secure the Y-site connection tubing to the administration tubing.



11. Infuse Vivaglobin – Follow the manufacturer's instructions to turn on the pump.

12. Record the infusion – Remove the peel-off portion of the label from each vial used, and affix it to the patient record.

After administration, immediately discard any unused product and administration equipment in accordance with local procedures.

3 DOSAGE FORMS AND STRENGTHS

Vivaglobin is a solution containing 16% IgG (160 mg/mL) for subcutaneous infusion.

4 CONTRAINDICATIONS

Vivaglobin is contraindicated in patients who have had an anaphylactic or severe systemic reaction to the administration of Immune Globulin (Human).

Vivaglobin is contraindicated in IgA-deficient patients with antibodies against IgA or a history of hypersensitivity (*see Description [11]*).

5 WARNINGS AND PRECAUTIONS

5.1 Hypersensitivity Reactions

Severe hypersensitivity reactions may occur (*see Patient Counseling Information [17.2]*). In case of hypersensitivity, discontinue the Vivaglobin infusion immediately and institute appropriate treatment. Epinephrine should be immediately available to treat any acute severe hypersensitivity reactions.

Individuals with IgA deficiency can develop anti-IgA antibodies and anaphylactic reactions (including anaphylaxis and shock) after administration of blood components containing IgA. Patients with known antibodies to IgA may have a greater risk of developing potentially severe hypersensitivity and anaphylactic reactions. Vivaglobin contains ≤1.7 mg/mL IgA (*see Description [11]*). The minimum concentration of IgA that will provoke a hypersensitivity reaction is not known; therefore all IgG preparations carry the risk of inducing an anaphylactic reaction to IgA.

5.2 Aseptic Meningitis Syndrome (AMS)

AMS has been reported to occur infrequently with IGIV treatment[5] and with Vivaglobin treatment. The syndrome usually begins within several hours to 2 days following IGIV treatment. AMS is characterized by signs and symptoms including severe headache, nuchal rigidity, drowsiness, fever, photophobia, painful eye movements, nausea, and vomiting. Cerebrospinal fluid (CSF) studies frequently show pleocytosis up to several thousand cells per cubic millimeter, predominantly from the granulocytic series, and with elevated protein levels up to several hundred mg/dL. AMS may occur more frequently in association with high doses (2 g/kg) and/or rapid infusion of IGIV.

Patients exhibiting such signs and symptoms should receive a thorough neurological examination, including CSF studies, to rule out other causes of meningitis. Discontinuation of IGIV treatment has resulted in remission of AMS within several days without sequelae.

5.3 Reactions Reported with IGIV Treatment

The following reactions have been reported to occur with IGIV treatment and may occur with IGSC treatment.

Renal Dysfunction/Failure

Renal dysfunction/failure, osmotic nephropathy, and death may occur with use of human immune globulin products. Ensure that patients are not volume depleted and assess renal function, including measurement of blood urea nitrogen (BUN) and serum creatinine, before the initial infusion of Vivaglobin and at appropriate intervals thereafter.

Periodic monitoring of renal function and urine output is particularly important in patients judged to have a potential increased risk of developing acute renal failure.[1] If renal function deteriorates, consider discontinuing Vivaglobin. For patients judged to be at risk of developing renal dysfunction because of pre-existing renal insufficiency or predisposition to acute renal failure (such as those with diabetes mellitus or hypovolemia, those who are overweight or use concomitant nephrotoxic medicinal products, or those who are over 65 years of age), administer Vivaglobin at the minimum rate practicable.

Thrombotic Events

Thrombotic events may occur with use of human immune globulin products.[2-4] Patients at risk may include those with a history of atherosclerosis, multiple cardiovascular risk factors, advanced age, impaired cardiac output, hypercoagulable disorders, prolonged periods of immobilization, and/or known or suspected hyperviscosity. Because of the potentially increased risk of thrombosis, consider baseline assessment of blood viscosity in patients at risk for hyperviscosity, including those with cryoglobulins, fasting chylomicronemia/markedly high triacylglycerols (triglycerides), or monoclonal gammopathies. For patients judged to be at risk of developing thrombotic events, administer Vivaglobin at the minimum rate practicable.

Hemolysis

Vivaglobin may contain blood group antibodies that may act as hemolysins and induce *in vivo* coating of red blood cells (RBCs) with immunoglobulin, causing a positive direct antiglobulin (Coombs') test result and hemolysis.[6-8] Delayed hemolytic anemia can develop subsequent to immune globulin therapy due to enhanced RBC sequestration, and acute hemolysis, consistent with intravascular hemoylysis, has been reported.[9]

Monitor recipients of Vivaglobin for clinical signs and symptoms of hemolysis. If these are present after Vivaglobin infusion, perform appropriate confirmatory laboratory testing. If transfusion is indicated for patients who develop hemolysis with clinically compromising anemia after receiving Vivaglobin, perform adequate cross-matching to avoid exacerbating on-going hemolysis.

Transfusion-Related Acute Lung Injury (TRALI)

Noncardiogenic pulmonary edema may occur in patients administered human immune globulin products.[10] TRALI is characterized by severe respiratory distress, pulmonary edema, hypoxemia, normal left ventricular function, and fever. Typically, it occurs within 1 to 6 hours following transfusion. Patients with TRALI may be managed using oxygen therapy with adequate ventilatory support.

Monitor recipients of Vivaglobin for pulmonary adverse reactions. If TRALI is suspected, perform appropriate tests for the presence of anti-neutrophil antibodies in both the product and patient's serum.

5.4 Transmissible Infectious Agents

Because Vivaglobin is made from human plasma, it may carry a risk of transmitting infectious agents, e.g., viruses and, theoretically, the Creutzfeldt-Jakob (CJD) agent. No cases of transmission of viral diseases or CJD have been associated with the use of Vivaglobin. Report all infections thought possibly to have been transmitted by Vivaglobin to the CSL Behring Pharmacovigilance Department at 1-866-915-6958 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*. The physician should discuss the risks and benefits of this product with the patient before prescribing or administering it to the patient (*see Patient Counseling Information [17.2]*).

5.5 Laboratory Tests

After infusion of IgG, 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, and D) may cause a positive direct or indirect antiglobulin (Coombs') test.

6 ADVERSE REACTIONS

The most common adverse reactions (those AEs considered by the investigator to be at least possibly related to Vivaglobin administration) observed in ≥5% of study subjects receiving Vivaglobin were local injection-site reactions (swelling, redness, and itching), headache, nausea, rash, asthenia, and gastrointestinal disorder.

6.1 Clinical Studies Experience

Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

US-Canada Study

The safety of Vivaglobin was evaluated in a clinical study in the US and Canada for 12

months in 65 subjects with PI who had been previously treated with IGIV every 3 or 4 weeks (*see Clinical Studies [14.1]*). After 3 months, subjects were switched from IGIV to weekly subcutaneous administration of Vivaglobin for 12 months. Subjects were treated weekly with Vivaglobin at a mean dose of 158 mg/kg body weight (range: 34 to 352 mg/kg). The 65 subjects received a total of 3,656 infusions of Vivaglobin.

Table 2 shows the number of subjects who withdrew from the US-Canada study due to adverse events (AEs) and the AEs leading to discontinuation.

Table 2: Subjects with Adverse Events (AEs) Leading to Discontinuation, US-Canada Study

AEs	Subjects with AEs *At Least Possibly Related*	Subjects with AEs *Irrespective of Causality*	Total Number (%) of Subjects
Subjects with at least 1 AE leading to discontinuation	4	1	5 (8%)
Injection-site reaction	3	–	3 (5%)
Intestinal obstruction	–	1	1 (2%)
Hyperventilation	1*	–	1 (2%)
Tachycardia	1*	–	1 (2%)

* One subject experienced hyperventilation and tachycardia.

Table 3 summarizes the most frequent AEs (experienced by more than 5% of subjects), *irrespective of causality*. It includes all AEs and those considered temporally associated with the Vivaglobin infusion, i.e., occurring during the infusion or within 72 hours after the end of the infusion.

Table 3: Incidence of Subjects With Adverse Events (AEs)* (Experienced by >5% of Subjects) and Rate† per Infusion, *Irrespective of Causality*, in the US-Canada Study

AEs* (>5% of Subjects)	All AEs		AEs Occurring During or Within 72 Hours of Infusion	
	Number (%) of Subjects (n=65)	Number (Rate†) of AEs per Infusion (n=3656)	Number (%) of Subjects (n=65)	Number (Rate†) of AEs Per Infusion (n=3656)
AEs at the injection site‡	60 (92%)	1789 (0.49)	60 (92%)	1767 (0.4848)
Other AEs				
Headache	31 (48%)	159 (0.04)	30 (46%)	104 (0.033)
Gastrointestinal disorder	24 (37%)	35 (0.01)	18 (28%)	24 (0.007)
Fever	16 (25%)	28 (0.008)	12 (8%)	20 (0.005)
Nausea	12 (18%)	18 (0.005)	11 (17%)	15 (0.004)
Rash	11 (17%)	22 (0.006)	10 (15%)	16 (0.004)
Sore throat	10 (15%)	17 (0.005)	8 (12%)	11 (0.003)
Allergic reaction	7 (11%)	8 (0.002)	5 (8%)	5 (0.001)
Pain	6 (9%)	8 (0.002)	4 (6%)	4 (0.001)
Diarrhea	6 (9%)	6 (0.002)	5 (8%)	5 (0.001)
Cough increased	6 (9%)	6 (0.002)	5 (8%)	5 (0.001)
Gastrointestinal pain	5 (8%)	6 (0.002)	4 (6%)	5 (0.001)
Migraine	5 (8%)	5 (0.001)	2 (3%)	2 (0.001)
Skin disorder	5 (8%)	7 (0.002)	3 (5%)	5 (0.001)
Asthma	5 (8%)	8 (0.002)	3 (5%)	4 (0.001)
Arthralgia	4 (6%)	4 (0.001)	3 (5%)	3 (0.001)
Asthenia	4 (6%)	4 (0.001)	2 (3%)	2 (0.001)
Malaise	4 (6%)	5 (0.001)	2 (3%)	2 (0.001)

* Excluding infections.
† Rate, number of AEs per infusion.
‡ Includes injection-site inflammation.

The total number of AEs, *irrespective of causality,* including injection-site reactions, that began during or within 72 hours after the end of an infusion was 2262 (a rate of 0.62 AEs per infusion); excluding injection-site reactions, the rate of AEs per infusion was 0.14.

Table 4 summarizes the severity of local AEs by infusion, *irrespective of causality*.

Table 4: Severity of Local Adverse Events (AEs) by Infusion, *Irrespective of Causality*, in the US-Canada Study

AEs (Number of infusions: 3656)	Number (Rate*) of AEs	Number (Rate*) of AEs Occurring During or Within 72 Hours of Infusion
AEs at the injection site	1789 (0.49)	1767 (0.48)
Mild†	1112 (0.30)	1100 (0.30)
Moderate‡	601 (0.16)	593 (0.16)
Severe§	65 (0.02)	64 (0.02)
Unknown severity	11 (<0.01)	10 (<0.01)
Discontinuations due to AEs at the injection site	3 subjects	

* Rate, number of AEs per infusion.
† Defined as those reactions that did not interfere with routine activities.
‡ Defined as those reactions that interfered with routine activities.
§ Defined as those reactions that made it impossible to perform routine activities.

Of the three subjects who discontinued the study due to injection-site reactions, one withdrew on Day 1 (Infusion 1) of the wash-in/wash-out period after a moderate injection-site reaction and a mild headache; one withdrew on Day 22 (Infusion 4) of the wash-in/wash-out period following severe injection-site reactions for two weeks; and one withdrew on Day 78 following a mild injection-site reaction.

Local reactions decreased substantially after repeated use.

Table 5 summarizes the most frequent adverse reactions (experienced by at least 3% of subjects) and considered by the investigator to be *at least possibly related* to Vivaglobin administration.

Table 5: Incidence of Subjects With Adverse Reactions (Experienced in ≥3% of Subjects) and Rate* Per Infusion in the US-Canada Study

Related Adverse Reactions (≥3% Subjects)	Number (%) of Subjects (n=65)	Number (Rate*) of Adverse Reactions per Infusion (n=3656)
Adverse reactions at the injection site†	60 (92%)	1787 (0.49)
Other Adverse reactions		
Headache	21 (32%)	59 (0.016)
Nausea	7 (11%)	9 (0.002)
Rash	4 (6%)	9 (0.002)
Asthenia	3 (5%)	3 (0.001)
Gastrointestinal disorder	3 (5%)	3 (0.001)
Fever	2 (3%)	2 (0.001)
Skin disorder	2 (3%)	3 (0.001)
Tachycardia	2 (3%)	2 (0.001)
Urine abnormality	2 (3%)	3 (0.001)

***** Rate, number of adverse reactions per infusion.
† Includes injection-site inflammation.

Europe-Brazil Study

In a clinical study conducted in Europe and Brazil, the efficacy and safety of Vivaglobin were evaluated for 10 months in 60 subjects with PI. Subjects were treated weekly with Vivaglobin at a mean dose of 89 mg/kg body weight (range: 51 to 147 mg/kg), which was 101% of their previous weekly IGIV or IGSC dose (*see Clinical Studies [14.2]*). Study subjects received a total of 2,297 infusions of Vivaglobin.

The AEs and their rates reported in this study were similar to those reported in the US-Canada study, with two exceptions: no episodes of headache were reported; and 18 (a rate of 0.008 per infusion) episodes of fever were judged to be related to the administration of Vivaglobin. One subject discontinued due to repeated local reactions of moderate severity.

6.2 Postmarketing Experience

Because postmarketing reporting of adverse reactions is voluntary and from a population of uncertain size, it is not always possible to reliably estimate the frequency of these reactions or establish a causal relationship to product exposure.

Vivaglobin

Adverse reactions identified during worldwide postmarketing use of Vivaglobin for treatment of PI are allergic-anaphylactic reactions (including dyspnea, pruritus, urticaria, rash, edema and other cutaneous reactions, wheezing, syncope, hypotension, and throat swelling), generalized reactions (including flu-like symptoms, myalgia, chills, fever, tachycardia, arthralgia, nausea and vomiting, diarrhea, gastrointestinal cramping, stomach pain, back pain, headache, headache possibly caused by increased blood pressure, and chest tightness), migraine, and injection-site reactions.

General
The following adverse reactions have been identified and reported during the postmarketing use of IGIV products[11]:

- *Renal:* Acute renal dysfunction/failure, osmotic nephropathy
- *Respiratory:* Apnea, Acute Respiratory Distress Syndrome (ARDS), TRALI, cyanosis, hypoxemia, pulmonary edema, dyspnea, bronchospasm
- *Cardiovascular:* Cardiac arrest, thromboembolism, vascular collapse, hypotension
- *Neurological:* Coma, loss of consciousness, seizures, tremor, aseptic meningitis syndrome
- *Integumentary:* Stevens-Johnson syndrome, epidermolysis, erythema multiforme, bullous dermatitis
- *Hematologic:* Pancytopenia, leukopenia, hemolysis, positive direct antiglobulin (Coombs') test
- *General/Body as a Whole:* Pyrexia, rigors
- *Musculoskeletal:* Back pain
- *Gastrointestinal:* Hepatic dysfunction, abdominal pain

7 DRUG INTERACTIONS

7.1 Live Virus Vaccines
The passive transfer of antibodies with immunoglobulin administration may interfere with the response to live virus vaccines such as measles/mumps/rubella and varicella (*see Patient Counseling Information [17.2]*).

7.2 Serological Testing
Various passively transferred antibodies in immunoglobulin preparations may lead to misinterpretation of the results of serological testing.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy
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 can affect reproduction capacity. Vivaglobin should be given to a pregnant woman only if clearly needed.

8.3 Nursing Mothers
Vivaglobin has not been evaluated in nursing mothers.

8.4 Pediatric Use
- In the US-Canada study, Vivaglobin was evaluated in 6 children (ages 5 through 11) and 4 adolescents (ages 13 through 16). In the Europe-Brazil study, Vivaglobin was evaluated in 16 children (ages 3 through 11) and 6 adolescents (ages 13 through 16).
- The safety and efficacy of Vivaglobin were not studied in pediatric subjects under 2 years of age.
- There were no differences in the safety and efficacy profiles as compared with adult subjects.
- No pediatric-specific dosing requirements were necessary to achieve the desired serum IgG levels.
- For recommendations on the number of simultaneous injection sites for pediatric patients who weigh less than 45 kg (99 pounds), *see Administration (2.4)*.

8.5 Geriatric Use
The clinical studies of Vivaglobin did not include sufficient numbers of subjects 65 years of age and older to determine whether they respond differently from younger subjects. For recommendations on the number of simultaneous injection sites for geriatric patients, see *Administration (2.4)*.

11 DESCRIPTION
Vivaglobin is a sterile solution consisting of pasteurized, polyvalent immune globulin for subcutaneous administration. Vivaglobin is manufactured from large pools of human plasma by cold alcohol fractionation and is not chemically altered or enzymatically degraded. Vivaglobin is a 16% (160 mg/mL) protein solution, with a content of at least 96% IgG. Vivaglobin contains ≤1.7 mg/mL IgA and ≤1.8 mg/mL IgM. The distribution of IgG subclasses is similar to that present in normal human plasma. Vivaglobin also 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 preservative.

All plasma units used in the manufacture of Vivaglobin have been tested using serological assays for hepatitis B surface antigen and antibodies to HIV-1/2 and HCV as well as Nucleic Acid Testing (NAT) for HIV-1 and HCV and found to be nonreactive (negative). For 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 HAV and B19V. Only plasma that passed virus screening is used for production, and the limit for B19V in the fractionation pool is set not to exceed 10^4 IU of B19V DNA per mL.

The capacity of the manufacturing process to remove and/or inactivate enveloped and non-enveloped viruses has been validated by laboratory spiking studies on a scaled-down process model, using enveloped and non-enveloped viruses. The virus reduction capacity of two steps (ethanol – fatty alcohol / pH precipitation and pasteurization in aqueous solution at 60°C for 10 hours) was evaluated. Total mean cumulative virus reductions ranged from 9.0 to ≥14.1 $\log_{10}$ as shown in Table 6.

Table 6: 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-1/2; BVDV, bovine viral diarrhea virus, model for HCV and 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 immune globulin product); CPV, canine parvovirus, model for B19V.
* Reduction of B19V (evaluated using porcine IgG) by pasteurization was ≥5.0 $\log_{10}$.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action
Vivaglobin supplies a broad spectrum of opsonizing and neutralizing IgG antibodies against a wide variety of bacterial and viral agents. The mechanism of action in PI has not been fully elucidated.

12.3 Pharmacokinetics
The bioavailability of Vivaglobin is approximately 73% compared with IGIV, but can vary significantly among patients (*see Clinical Studies [14.1]*). With Vivaglobin, peak serum IgG levels are lower than those achieved with IGIV. Subcutaneous administration results in relatively stable steady-state serum IgG levels when the product is dosed on a weekly basis.[12-13]

The pharmacokinetics (PK) of Vivaglobin were evaluated in the clinical study conducted in the US and Canada (*see Clinical Studies [14.1]*). Subjects previously treated with IGIV were switched to weekly subcutaneous treatment with Vivaglobin. After a 3-month wash-in/wash-out period, doses were adjusted individually aiming to provide an IgG systemic exposure (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 dose adjustment for Vivaglobin was 137% ± 21% SD (range: 103% to 192%) of the previous weekly-equivalent IGIV dose. Following 10 to 12 weeks of treatment with Vivaglobin at this individually adjusted dose, the final steady-state AUC determinations were made in 17 of the 19 per-protocol subjects. 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 17 subjects.

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: Additional Pharmacokinetic Parameters, US-Canada Study

	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.

The 6-month clinical study conducted in Europe and Brazil in 60 subjects with PI also included a PK evaluation. Subjects were treated weekly with Vivaglobin at a mean dose of 89 mg/kg body weight (range: 51 to 147 mg/kg), which was 101% of their previous weekly IGIV or IGSC dose (*see Clinical Studies [14.2]*). After the subjects had reached steady state with weekly administration of Vivaglobin, peak serum IgG levels were observed after a mean of 2.5 days (range: 0 to 7 days) in 41 subjects.

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

14 CLINICAL STUDIES

14.1 US-Canada Study
The open-label, prospective, multicenter clinical study conducted in the US and Canada evaluated the pharmacokinetics, efficacy, safety, and tolerability of Vivaglobin in 65 (51

per-protocol) adult and pediatric subjects with PI. Subjects previously receiving monthly treatment with IGIV were switched to weekly subcutaneous administration of Vivaglobin for 12 months, after a 3-month wash-in/wash-out period.

The study evaluated the annual rate of serious bacterial infections (defined as bacterial pneumonia, meningitis, sepsis, osteomyelitis, and visceral abscesses). The annual rate of any infections was also evaluated.

In this study, the volume of Vivaglobin infused (using administration tubing and an infusion pump) did not exceed 15 mL per injection site at a rate of 20 mL per hour per site. Doses greater than 15 mL were divided and infused into multiple sites using Y-site connection tubing. For recommendations on the number of simultaneous injection sites for pediatric patients weighing less than 45 kg (99 pounds), see *Administration (2.4)*.

Table 8 summarizes the dosing and annual rate of infections for the 51 per-protocol subjects in efficacy phase of the US-Canada study.

Table 8: Dose and Annual Rate of Infections with Vivaglobin – Per-protocol Subjects, Efficacy Phase of the US-Canada Study

Number of per-protocol subjects (efficacy phase)	51
Weekly dose of Vivaglobin	
Mean	158 mg/kg bw
Range	34-352 mg/kg bw
Mean % previous IGIV dose (range)	136%* (99%-188%)
Annual rate of serious bacterial infections	0.04 infections/subject year†,‡
Annual rate of any infections	4.4 infections/subject year

bw, body weight.
* Actual mean of the median subcutaneous dose administered in the 12-month efficacy phase.
† One-sided upper 99% confidence interval: 0.14%.
‡ Pneumonia was reported in two subjects.

Table 9 provides a summary of missed school or work and hospitalization due to infection, which were also evaluated in the efficacy phase of the study.

Table 9: Additional Efficacy Results – Per-protocol Subjects, US-Canada Study

Number of per-protocol subjects (efficacy phase)	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

14.2 Europe-Brazil Study

In a clinical study of Vivaglobin conducted in Europe and Brazil, 60 adult and pediatric subjects with PI were switched to weekly subcutaneous administration of Vivaglobin for 6 months. Forty-nine (49) subjects had been on IGIV, and 11 subjects had been treated long-term with another IGSC before entering the study. The 47 per-protocol subjects received a weekly mean dose of 89 mg/kg body weight of Vivaglobin (range: 51 to 147 mg/kg), which was 101% (range: 81% to 146%) of their previous immune globulin treatment.

The annualized rate of serious bacterial infections was 0.04 infections per subject year (one-sided upper 99% confidence interval: 0.21). The annualized rate of any infections was 4.3 infections per subject year).

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16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

Vivaglobin is supplied in a single-use, tamper-evident vial containing 160 mg protein per mL of preservative-free liquid. Each vial label contains a peel-off strip with the vial size and product lot number for use in recording doses in a patient treatment record. The components used in the packaging for Vivaglobin are latex-free.

The following dosage forms are available:

NDC Number	Vial Size	Packaging	Grams Protein
0053-7596-01	3 mL	Single vial	0.48 g
0053-7596-10	10 mL	Single vial	1.6 g
0053-7596-20	20 mL	Single vial	3.2 g

16.2 Storage and Handling

Store in the refrigerator at 2–8°C (36–46°F). Vivaglobin is stable for the period indicated by the expiration date on its label. Do not freeze. Do not use product that has been frozen. Do not shake. Keep Vivaglobin in its original carton to protect it from light.

17 PATIENT COUNSELING INFORMATION

17.1 Self-Administration

If self-administration is appropriate, ensure that the patient receives instructions and training on subcutaneous administration in the home setting. This should include the type of equipment to be used and information on its maintenance, demonstration of proper infusion techniques, selection of appropriate infusion sites (e.g., abdomen, thigh, upper arm, and/or lateral hip), maintenance of a treatment diary/log book, and measures to be taken in case of adverse reactions.

Make sure your patients understand how important it is that they adhere to the weekly administration schedule for Vivaglobin in order to maintain the steady levels of IgG in their blood. It is recommended that patients keep their treatment diary/log book current by recording, after each infusion, the time, date, dose, and any reactions, and by removing the peel-off portion of the label (containing the lot number) from the product vial and placing it in the treatment diary/log book.

Tell your patients that mild to moderate local injection-site reactions (e.g., swelling, redness, and itching) are a common side effect of subcutaneous therapy, but to contact their healthcare professional if a local reaction lasts longer than 4 days or is severe. With subcutaneous infusions, it is important that the needle is long enough to reach the subcutaneous tissue and that the actual point of injection be changed with each infusion.

17.2 Additional Information for Patients

- **Dose adjustments** – Tell patients that they may be tested regularly to make sure they have the correct levels of Vivaglobin (IgG) in their blood. These tests may result in adjustments to their dose.
- **Hypersensitivity reactions** – Inform patients of the early signs of hypersensitivity reactions to Vivaglobin (including hives, generalized urticaria, tightness of the chest, wheezing, hypotension, and anaphylaxis). Advise them of appropriate actions to take in the event of a hypersensitivity reaction.
- **Interference with vaccines** – Inform patients that administration of immunoglobulin may interfere with the response to live virus vaccines (e.g., measles, mumps, rubella, and varicella) and to notify their immunizing physician of recent therapy with Vivaglobin.
- **Aseptic meningitis syndrome (AMS)** – Inform patients of the symptoms of AMS, including severe headache, neck stiffness, drowsiness, fever, sensitivity to light, painful eye movements, nausea, and vomiting.
- **Reactions reported with IGIV treatment** – Advise patients to be aware of and immediately report the following signs and symptoms to their healthcare professional:
- Decreased urine output, sudden weight gain, fluid retention/edema, and/or shortness of breath, which may suggest kidney problems.
- Shortness of breath, changes in mental status, chest pain, and other manifestations of thrombotic and embolic events.
- Fatigue, increased heart rate, yellowing of the skin or eyes, and dark-colored urine, which may suggest hemolysis.
- Severe breathing problems, lightheadedness, drops in blood pressure, and fever, which may suggest TRALI (a condition typically occurring within one to six hours following transfusion).
- **Transmissible infectious agents** – Inform patients that Vivaglobin is made from human plasma (part of the blood) and may contain infectious agents that can cause disease.

The attached Vivaglobin "Information for Patients" contains more detailed instructions for patients who will be self-administering Vivaglobin.

FDA-Approved Patient Labeling
Vivaglobin® (Pronounced VEE-vah-glow-bin)
Immune Globulin Subcutaneous (Human)
Information for patients

This leaflet contains important information about Vivaglobin. *Please read it carefully before using this medicine.* This information does not take the place of talking with your healthcare professional, and it does not include all of the available information about Vivaglobin. If you have any questions after reading this, ask your healthcare professional.

What is the most important information I should know about Vivaglobin?

- Vivaglobin is supposed to be infused under your skin only. DO NOT inject Vivaglobin into a blood vessel (vein or artery).

What is Vivaglobin?

Vivaglobin is a solution that contains proteins, called immunoglobulins, from plasma (the liquid part of human blood). These proteins are used to treat primary immunodeficiency (also called PI). People with primary immunodeficiency get a lot of infections because their immune system doesn't function properly.

Vivaglobin contains the antibody immunoglobulin G (IgG), which helps your body fight off infections caused by bacteria and viruses. Vivaglobin contains no preservatives, and the packaging contains no latex.

Who should <u>NOT</u> take Vivaglobin?

Do not take Vivaglobin if you have had a hypersensitivity reaction or a serious allergic reaction to other immunoglobulin medicines.

Tell your doctor if you have a condition called selective (or severe) immunoglobulin A (IgA) deficiency. This may mean you have a much greater chance of having an allergic reaction to Vivaglobin.

Tell your doctor if you have a history of heart or blood vessel disease or blood clots, have thick blood, or have been immobile for some time. These things may increase your risk of having a blood clot after using Vivaglobin.

How should I take Vivaglobin?

You will use a needle to infuse Vivaglobin under your skin. Do not use Vivaglobin until you have been taught how to infuse it. For the treatment to work properly, you must follow the dose and treatment schedule that your doctor gives you. Your doctor will obtain blood samples regularly to make sure you are getting the right amount of Vivaglobin.

Carefully read the "Instructions for Use" located at the end of this leaflet before you start your infusion. If you have any questions about the "Instructions for Use," discuss them with your doctor before you start to use Vivaglobin.

What should I avoid while taking Vivaglobin?

Vivaglobin can make some vaccines (like measles/mumps/rubella or chickenpox vaccines) not work as well for you. Before you get any vaccines, tell your doctor or healthcare professional that you take Vivaglobin.

Do not mix other products with the Vivaglobin solution.

Tell your doctor if you are pregnant or plan to become pregnant, or if you are nursing.

What are possible side effects of Vivaglobin?

The most common side effects with Vivaglobin occur in the area of the skin where the infusion needle is placed. These include redness, itching, swelling, and pain. Most of these side effects go away within 1 to 2 days. Tell your doctor if any of these side effects last for 4 days or more. These side effects may happen less and less with continued regular use of Vivaglobin.

Other side effects that might occur include:

- Headache/migraine
- Upset stomach
- Cramps
- Diarrhea
- Fever
- Nausea
- Sore throat
- Rash
- Pain
- Cough
- Fast heart rate
- Chest tightness
- Back pain
- Joint pain
- Muscle ache

Tell your doctor right away or go to the emergency room if you have hives, trouble breathing, wheezing, dizziness, or fainting. These could be signs of a bad allergic reaction.

Tell your doctor right away if you get any of the following symptoms. They could be signs of a serious problem.

- Reduced urination, sudden weight gain, or swelling in your legs. These could be signs of a kidney problem.
- Pain, swelling, warmth, redness, or a lump in your legs or arms. These could be signs of a blood clot.
- Bad headache with nausea, vomiting, stiff neck, fever, and sensitivity to light. These could be signs of a brain swelling called meningitis.
- Brown or red urine, fast heart rate, yellow skin or eyes. These could be signs of a blood problem.
- Chest pain or trouble breathing.
- Fever over 100ºF. This could be a sign of an infection.

Tell your doctor about any side effects that concern you. You can ask your doctor to give you more information that is available to healthcare professionals.

How do I use Vivaglobin?

Vivaglobin is infused under the skin (subcutaneously). With proper training, you can infuse it on your own. Do not inject Vivaglobin into a blood vessel (vein or artery).

Your doctor will determine the appropriate dose and schedule for your treatment.

Your healthcare professional will teach you how to infuse Vivaglobin. Always follow the instructions you receive. The instructions below are general guidelines for using Vivaglobin. Use them only as an aid once you have learned the proper way to infuse Vivaglobin. Call your healthcare professional if you are not sure about the procedure or if you have any questions about these instructions.

Instructions for use

Do not use Vivaglobin until you have been taught how to use it by your doctor. For the treatment to work, you must carefully follow your doctor's instructions. The instructions below are provided to you as a guide. If you have any questions about these instructions, it is important that you discuss them with your doctor before you start to use Vivaglobin.

Keep Vivaglobin and all other medicines away from children.

Vivaglobin comes in single-use vials. Keep these vials in their storage box in the refrigerator at 2-8°C (36-46°F) until you are ready to use them. Do not freeze. Vivaglobin has no preservatives added, so it is important to throw away any Vivaglobin leftover in a vial after it is opened.

1. Take the Vivaglobin vial(s) out of the refrigerator and let it warm up to room temperature. Clean a table or other flat surface. Get together all of the supplies you need for your infusion. Generally, you will need:
   - Vivaglobin vial(s)
   - Treatment diary or logbook
   - Infusion pump
   - Infusion administration tubing
   - Needle or catheter sets (for subcutaneous infusion)
   - Y-site connectors (if needed)
   - Alcohol wipes
   - Antiseptic skin preps
   - Syringes
   - Transfer needles
   - Gauze and tape, or transparent dressing
   - Transparent dressing
   - Sharps container
   - Gloves (if recommended by your healthcare professional)
2. Thoroughly wash and dry your hands (Figure 1). If you have been told to wear gloves when preparing your infusion, put the gloves on.

Figure 1

3. Carefully look at the liquid in each vial of Vivaglobin (Figure 2). It should look clear and be colorless to light brown. Check for particles or color changes. Do not use the vial if:

- The liquid looks cloudy, contains particles, or has changed color.
- The protective cap is missing.
- The expiration on the label has passed.

4. Take the protective cap off of each vial (Figure 3).

5. Clean each vial stopper with an alcohol wipe (Figure 4). Let the stopper dry.

6. Using aseptic technique as instructed by your healthcare professional, attach a transfer needle to the syringe tip (Figure 5).

7. Transfer the Vivaglobin from the vial to the syringe as follows:

- Pull out the plunger on the syringe to fill it with air. The amount of air should be the same as the amount of Vivaglobin you will transfer from the vial.
- Put the Vivaglobin vial on a flat surface. Keeping the vial upright, insert the transfer needle into the center of the rubber stopper.
- Check that the tip of the needle is not in the liquid. Then, push the plunger on the syringe down. This will inject the air from the syringe into the airspace of the vial.
- Leaving the needle and syringe in the stopper, carefully turn the vial upside down (Figure 6).
- Slowly pull back on the plunger to fill the syringe with Vivaglobin.
- Take the filled syringe and needle out of the stopper. Take off the needle and throw it away in the sharps container.

If you are using more than one vial, your healthcare professional will show you how to fill the syringe before starting the infusion.

8. Prepare the infusion pump (following the manufacturer's instructions) and prime the administration tubing (Figure 7). To prime the tubing, connect the syringe filled with Vivaglobin to the administration tubing and gently push on the syringe plunger to fill the tubing with Vivaglobin.

9. Select an area on your abdomen, thigh, upper arm, or on the side of upper leg/hip for the infusion (Figure 8). Do not insert the needle in the same place it was the last time you infused Vivaglobin.

- Your healthcare professional will help you decide which part of your body is best for infusion.
- Your healthcare professional will tell you how many injection sites you need to use and how much Vivaglobin to infuse at each site. Generally, doses more than 15 mL should be divided and infused at a different site.
- Do not use more than 3 injection sites at the same time if you are a child weighing less than 99 pounds, more than 6 sites at the same time of you are under age 65, or more than 4 sites at the same time if you are over age 65. If needed, you can use more injection sites consecutively.

Figure 2

Figure 3

Figure 4

Figure 5

Figure 6

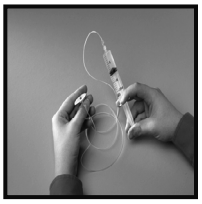

Figure 7

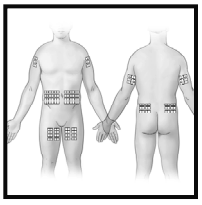

Figure 8

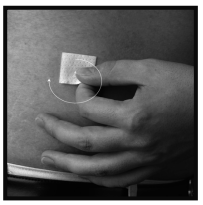

Figure 9

- If you are using more than one injection site, be sure that each site is at least 2 inches apart.

Clean the skin at each site with an antiseptic skin prep (Figure 9). Let the skin dry.

10. Depending on your body mass, use your thumb and forefinger to either pinch together the skin around the injection site or spread and flatten the skin around the injection site. Insert the needle under the skin (Figure 10).

11. After you have inserted the infusion needle, put sterile gauze and tape or a transparent dressing over the injection site (Figure 11). This will keep the needle from coming out.

12.. Do not inject Vivaglobin into a blood vessel. To test for this, attach a sterile syringe to the end of the administration tubing. Pull the plunger back gently (Figure 12). If you see any blood in the tubing, take the needle out of the injection site. Throw away the administration tubing and needle and start over at a different site with new administration tubing and a new needle.

13. Follow the instructions on the infusion pump (Figure 13) to connect the administration tubing and set the infusion rate. (Your doctor will tell you what rate to use for your Vivaglobin infusion. Generally, you will not infuse faster than 20 mL per hour per site.) Turn on the pump.

14. Peel off the removable part of the label from the Vivaglobin vial(s). Put this label in your treatment diary or logbook with the date and time of the infusion and the exact amount of Vivaglobin that you infused (Figure 14).

15. When all the Vivaglobin has been infused, turn off the pump. Take off the dressing and take the needle out of the injection site. Throw away the used supplies in the sharps container as directed by your healthcare professional (Figure 15).

16. Clean and store the infusion pump, following the manufacturer's care instructions.

Be sure to tell your doctor about any problems you have doing your infusions. Your doctor may ask to see your treatment diary or logbook, so be sure to take it with you each time you visit the doctor's office.

Call your doctor for medical advice about side effects. You can also report side effects to the FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch.*

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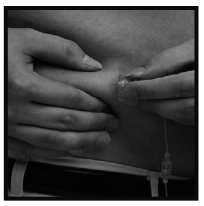

Figure 10

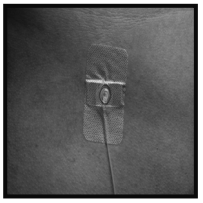

Figure 11

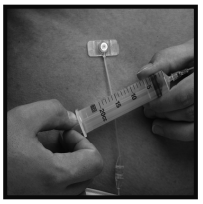

Figure 12

Figure 13

Figure 14

Figure 15