Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Vivaglobin, 160 mg/ml solution for injection (subcutaneous use).

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml contains:

human normal immunoglobulin (subcutaneous) 160 mg,

one vial contains:

480 mg/3 ml or 1600 mg/10 ml or 3200 mg/20 ml of human normal immunoglobulin,

one ampoule contains:

800 mg/5 ml of human normal immunoglobulin,

corresponding to the total protein content of which at least 95 % is IgG.

Distribution of IgG subclasses:

IgG_1 ca. 61 %

IgG_2 ca. 28 %

IgG_3 ca. 5 %

IgG_4 ca. 6 %

IgA max. 1.7 mg/ml

Excipient:

Sodium (as chloride and hydroxide): 0.8 to 1.6 mg/ml (35 to 70 mmol/L)

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection (subcutaneous use)
Vivaglobin is a clear solution. The colour can vary from colourless to pale yellow up to light brown during shelf life.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Replacement therapy in adults and children in primary immunodeficiency (PID) syndromes such as:

- congenital agammaglobulinaemia and hypogammaglobulinaemia
- common variable immunodeficiency
- severe combined immunodeficiency
- IgG subclass deficiencies with recurrent infections

Replacement therapy in myeloma or chronic lymphatic leukaemia with severe secondary hypogammaglobulinaemia and recurrent infections.

4.2 Posology and method of administration

Posology
The dosage may need to be individualized for each patient dependent on the pharmacokinetic and clinical response. The following dosage regimens are given as a guideline. The dosage regimen using the subcutaneous route should achieve a sustained plasma level of IgG.

A loading dose of at least 0.2 to 0.5 g/kg (1.3 to 3.1 ml/kg) body weight - divided over several days with a maximal daily dose of 0.1 to 0.15 g/kg bodyweight and as indicated by the treating physician - may be required. After steady state IgG levels have been attained, maintenance doses are administered at repeated intervals, ideally weekly, to reach a cumulative monthly dose of about 0.4 to 0.8 g/kg (2.5 to 5 ml/kg) body weight.

Trough levels of IgG should be measured in order to adjust the dose and dosage interval of Vivaglobin.

Method of administration
Vivaglobin should be administered via the subcutaneous route *(see section 3. "Pharmaceutical form" and 6.6 "Special precautions for disposal and other handling").*

Subcutaneous infusion for home treatment should be initiated and monitored by a physician experienced in the treatment of immunodeficiency and in the guidance of patients for home treatment. The patient will be instructed in the use of a syringe driver, infusion techniques, the keeping of a treatment diary and measures to be taken in case of severe adverse events. The recommended infusion rate is 22 ml/hour. In a clinical study with 53 patients evaluated, during the training phase under supervision of a physician, the infusion rate of Vivaglobin was increased from initially 10 ml to 22 ml/hour.

Vivaglobin should preferentially be administered in the abdominal wall, thigh and/or buttocks. No more than 15 ml should be injected into a single site. Doses over 15 ml should be divided and injected into 2 or more sites.

4.3 Contraindications

Hypersensitivity to any of the components of the product.
Vivaglobin must not be given intravascularly.
It must also not be administered intramuscularly in case of severe thrombocytopenia and in other disorders of haemostasis.

4.4 Special warnings and precautions for use

Do not inject intravascularly! If Vivaglobin is accidentally administered into a blood vessel, patients could develop anaphylactic shock or thromboembolic events.

The recommended infusion rate of Vivaglobin stated under "4.2 Method of administration" should be adhered to. Patients should be closely monitored and carefully observed for any adverse event throughout the infusion period.

Certain adverse reactions may occur more frequently in patients who receive human normal immunoglobulin for the first time or, in rare cases, when the product is switched or when treatment has been interrupted for more than eight weeks.

True hypersensitivity reactions are rare. They can occur in the very rare cases of IgA deficiency with anti-IgA antibodies and these patients should be treated with caution.

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

Potential complications can often be avoided by ensuring:

- that patients are not sensitive to human normal immunoglobulin, by first infusing the product slowly (see “4.2 Method of administration”);

- that patients are carefully monitored for any symptoms throughout the infusion period. In particular, patients should be monitored during the first infusion and for the first hour thereafter, in order to detect potential adverse reactions in the following situations:

  - patients naïve to human normal immunoglobulin,

  - patients switched from an alternative product or

  - when there has been a long interval since the previous infusion.

All other patients should be observed for at least 20 minutes after administration.

On suspicion of an allergic or anaphylactic reaction the administration has to be discontinued immediately. In case of shock the current medical standards for shock treatment have to be applied.

Thromboembolic Events
Arterial and venous thromboembolic events including myocardial infarction, stroke, deep venous thrombosis and pulmonary embolism have been associated with the use of Vivaglobin. Caution should be exercised in prescribing Vivaglobin in patients with preexisting risk factors for thrombotic events (such as advanced age, hypertension, diabetes mellitus and a history of vascular disease or thrombotic episodes, patients with acquired or inherited thrombophilic disorders, patients with prolonged periods of immobilization, severely hypovolemic patients, patients with diseases which increase blood viscosity).
Patients should be informed about first symptoms of thromboembolic events including shortness of breath, pain and swelling of a limb, focal neurological deficits and chest pain and should be advised to contact their physician immediately upon onset of symptoms.
Patients should be sufficiently hydrated before use of Vivaglobin.

Important information about some of the ingredients of Vivaglobin

This medicine contains up to 110 mg (4.8 mmol) sodium per dose (bodyweight 75 kg) if the maximal daily dose (11.25 g = 70.3 ml) is applied. To be taken into consideration in patients on a controlled sodium diet.

Virus safety

Standard measures to prevent infections resulting from the use of medicinal products prepared from human blood or plasma include selection of donors, screening of individual donations and plasma pools for specific markers of infection and the inclusion of effective manufacturing steps for the inactivation/removal of viruses. Despite this, when medicinal products prepared from human blood or plasma are administered, the possibility of transmitting infective agents cannot be totally excluded. This also applies to unknown or emerging viruses and other pathogens.

The measures taken are considered effective for enveloped viruses such as HIV, HBV and HCV, and for the non-enveloped viruses HAV and parvovirus B19.

There is reassuring clinical experience regarding the lack of hepatitis A or parvovirus B19 transmission with immunoglobulins and it is also assumed that the antibody content makes an important contribution to the virus safety.

It is strongly recommended that every time that Vivaglobin is administered to a patient, the name and batch number of the product are recorded in order to maintain a link between the patient and the batch of the product.

4.5 Interaction with other medicinal products and other forms of interaction

Live attenuated virus vaccines

Immunoglobulin administration may impair for a period of at least 6 weeks and up to 3 months the efficacy of live attenuated virus vaccines such as measles, rubella, mumps and varicella vaccines. After administration of Vivaglobin, an interval of at least 3 months should elapse before vaccination with live attenuated virus vaccines.
In the case of measles, this impairment may persist for up to 1 year. Therefore, patients receiving measles vaccine should have their antibody status checked.

Interference with serological testing
It has to be considered that when serological test results are interpreted, the transitory rise of passively transferred antibodies after immunoglobulin injections may result in misleading positive test results.

Passive transmission of antibodies to erythrocyte antigens, e.g. A, B and D may interfere with some serological tests for red cell allo-antibodies (e.g. Coombs test), reticulocyte count and haptoglobin.

4.6 Fertility, pregnancy and lactation

The safety of this medicinal product for use in human pregnancy has not been established in controlled clinical trials and therefore should only be given with caution to pregnant women or breast-feeding mothers. Clinical experience with immunoglobulins suggests that no harmful effects on the course of pregnancy, or on the foetus and the neonate are to be expected.

4.7 Effects on ability to drive and use machines

There are no indications that Vivaglobin may impair the ability to drive or use machines.

4.8 Undesirable effects

In a clinical study with s.c. administration in 60 subjects the following undesirable effects have been reported.

The following standard categories of frequency are used:

Very common	≥ 1/10
Common	≥ 1/100 and < 1/10
Uncommon	≥ 1/1,000 and < 1/100
Rare	≥ 1/10,000 and < 1/1,000
Very rare	< 1/10,000 (including reported single cases)

- ***Local reactions at the injection/infusion site:***

Very common: swelling, soreness, redness, induration, local heat, itching, bruising or rash.
The frequency declined very rapidly within the first ten infusions, when patients became used to the subcutaneous form of treatment. (In study patients who were treated with subcutaneous immunoglobulin for years before the trial, injection site reactions were not reported.)

- ***Immune system disorders***

In single cases: Allergic reactions including fall in blood pressure

- ***General disorders***

In single cases: Generalized reactions such as chills, fever, headache, malaise, moderate back pain, syncope, dizziness, rash, bronchospasm

Adverse reactions reported from post marketing surveillance are similar to the reactions which have also been observed during the clinical trials as listed above. In addition, the following have also been reported during post marketing surveillance:

- ***Immune system disorders***

Allergic/anaphylactic reactions including dyspnoea, cutaneous reactions, in isolated cases reaching as far as

anaphylactic shock, even when the patient has shown no hypersensitivity to previous administration

- ***General disorders***

Generalized reactions such as nausea, vomiting, arthralgia, headache possibly caused by increased blood pressure

- ***Nervous system disorders***

Migraine

- ***Vascular disorders***

Arterial and venous thromboembolic events including myocardial infarction, stroke, deep venous thrombosis and pulmonary embolism.
Cardiovascular reactions particularly if the product has been inadvertently injected intravascularly.

For information on infectious disease risk see 4.4 subsection “Virus safety”.

4.9 Overdose

Consequences of an overdose are not known.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: immune sera and immunoglobulins: immunoglobulins, normal human, for extravascular administration, ATC code: J06B A01
Human normal immunoglobulin contains mainly immunoglobulin G (IgG) having a broad spectrum of antibodies against various infectious agents.
Vivaglobin contains the immunoglobulin G antibodies present in the normal population. It is usually prepared from pooled plasma of at least 1,000 donors. It has a distribution of immunoglobulin G subclasses closely proportional to that in native human plasma. Adequate doses of this medicinal product may restore abnormally low immunoglobulin G levels to the normal range.

5.2 Pharmacokinetic properties

With subcutaneous administration for human normal immunoglobulin, peak levels are achieved in the recipient's circulation after a delay of approximately 2 days. Data from a clinical study (n=60) show that trough levels of approximately 8 to 9 g/l (n=53) in the plasma can be maintained by weekly doses between 0.05 and 0.15 g (0.3 to 0.9 ml/kg) Vivaglobin per kg bodyweight. This is commensurate to a monthly cumulative dosage of 0.2 to 0.6 g per kg body weight.
IgG and IgG-complexes are broken down in cells of the reticuloendothelial system.

5.3 Preclinical safety data

There are no preclinical data considered relevant to clinical safety beyond data included in other sections of the SPC.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Glycine, sodium chloride, hydrochloric acid or sodium hydroxide (for pH adjustment), water for injections

6.2 Incompatibilities

In the absence of compatibility studies this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

3 years.
Once an injection vial has been opened the solution should be used immediately.

6.4 Special precautions for storage

Store in a refrigerator (+2 °C to +8 °C) in the outer carton in order to protect from light. Do not freeze!
The product may be stored at room temperature (up to 25 °C) for a limited period of three months or until the expiry date (whichever date comes first) without being refrigerated again during this period. The new expiry date at room temperature should be noted on the carton. At the end of this period the product has to be used or discarded.

6.5 Nature and contents of container

3 ml of solution in a vial (Type I glass) with a stopper (chlorobutyl) – pack of 1 or 10 vials
10 ml of solution in a vial (Type I glass) with a stopper (chlorobutyl) – pack of 1 or 2 or 10 or 20 vials
20 ml of solution in a vial (Type I glass) with a stopper (chlorobutyl) – pack with 1 or 10 or 20 vials

Only the pack of 2 x 10 ml includes the following devices:
1 20 ml syringe
1 perfusor-tubing with needle
2 hypodermic needles
2 aeration needles
3 alcohol swabs

Not all pack sizes may be marketed.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

Vivaglobin is a ready for use solution and should be administered at body temperature. Do not use solutions that are cloudy or have deposits. The product must be inspected visually prior to administration and should not be used if there is any variation of physical appearance *(see also section 3 "Pharmaceutical form").*

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

7 MARKETING AUTHORISATION HOLDER

CSL Behring GmbH
Emil-von-Behring-Str.76
35041 Marburg
Germany

8 MARKETING AUTHORISATION NUMBER

PA 800/4/2

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 20 May 2005
Date of last renewal: 02 June 2009

10 DATE OF REVISION OF THE TEXT

May 2011