Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

SUBCUVIA 160 g/l. Solution for injection.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Human Normal Immunoglobulin (SCIg and IMIg)
One ml contains:

Human normal immunoglobulin …… 160 mg
(purity of at least 95% IgG)

Each vial of 5 ml contains 0.8 g of human normal immunoglobulin

Each vial of 10 ml contains 1.6 g of human normal immunoglobulin

Distribution of the IgG subclasses (approx. values):

IgG1 45-75%
IgG2 20-45%
IgG3 3-10%
IgG4 2-8%

The maximum IgA content is 4800 micrograms/ml

Produced from plasma of human donors.

Excipient with known effects:

This medicinal product contains 1.4 mg sodium per ml.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection
The product is a clear or slightly opalescent, colourless to pale yellow solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Replacement therapy in adults, children and adolescents (0-18) in:

- Primary immunodeficiency syndromes with impaired antibody production (see section 4.4)
- Hypogammaglobulinaemia and recurrent bacterial infections in patients with chronic lymphocytic leukemia (CLL), in whom prophylactic antibiotics have failed or are contra-indicated.
- Hypogammaglobulinaemia and recurrent bacterial infections in multiple myeloma (MM) patients
- Hypogammaglobulinaemia in patients pre- and post- allogenic haematopoietic stem cell transplant (HSCT)

4.2 Posology and method of administration

Replacement therapy should be initiated and monitored under the supervision of a physician experienced in the treatment of immunodeficiency.

Posology

The dose and dose regimen are dependent on the indication.

Replacement therapy

The medicinal product should be administered via the subcutaneous route.

In replacement therapy the dose may need to be individualized for each patient dependent on the pharmacokinetic and clinical response. The following dose regimens are given as a guideline.

The dosage regimen should achieve a trough level of IgG (measured before the next infusion) of at least 5 to 6 g/l and aim to be within the reference interval of serum IgG for age. A loading dose of at least 0.2 to 0.5 g/kg body weight may be required. This may need to be divided over several days, with a maximal daily dose of 0.1 to 0.15 g/kg.

After steady state IgG levels have been attained, maintenance doses are administered at repeated intervals (approximately once per week) to reach a cumulative monthly dose of the order of 0.4-0.8 g/kg. Each single dose may need to be injected at different anatomic sites.

Trough levels should be measured and assessed in conjunction with the incidence of infection. To reduce the rate of infection, it may be necessary to increase the dose and aim for higher trough levels.

SUBCUVIA may also be injected by the intramuscular route. In such cases, the cumulative monthly dose should be divided up into weekly or bi-weekly applications, in order to keep the injected volume low. To further minimize the discomfort for the patient, each single dosage may need to be injected at different anatomic sites.

Paediatric population

The posology in children and adolescents (0-18 years) is not different to that of adults as the posology for each indication is given by body weight and adjusted to the clinical outcome in replacement therapy indications.

Method of administration

SUBCUVIA should be administered via the subcutaneous route. In exceptional cases, where the subcutaneous administration is not possible, SUBCUVIA can be given intramuscularly.

Subcutaneous infusion for home treatment should be initiated and monitored by a physician experienced in the guidance of patients for home treatment. The patient must be instructed in the use of a syringe driver, the infusion techniques, the keeping of treatment diary, recognition of and measures to be taken in case of severe adverse reactions.

SUBCUVIA may be injected into sites such as abdomen, thigh, upper arm, and lateral hip.

It is recommended to use an initial administration speed of 10 ml/h/pump.

If well tolerated (see section 4.4), the infusion speed can be enhanced for 1ml/h/pump every subsequent infusion. The recommended maximum speed is 20 ml/h/pump. More than one pump can be used simultaneously. The infusion site should be changed every 5-15 ml. In adults doses over 30 ml may be divided according to patient preference. There is no limit to the number of infusion sites.

Intramuscular injection must be given by a physician or nurse.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1 (see section 4.4)

SUBCUVIA must not be given intravascularly.

SUBCUVIA must not be administered intramuscularly in cases of severe thrombocytopenia and in other disorders of haemostasis.

4.4 Special warnings and precautions for use

If SUBCUVIA is accidentally administered into a blood vessel, patients could develop shock.

The recommended infusion rate given under section 4.2 must be closely followed. Patients must be closely monitored and carefully observed for any symptoms 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 human normal immunoglobulin product is switched or when treatment has been stopped for more than eight weeks.

Potential complications can often be avoided by:

- Initially injecting the product slower than the regular recommended rate
- Ensuring that patients are carefully monitored for any symptoms throughout the infusion period. In particular, patients naïve to human normal immunoglobulin, patients switched from an alternative product or when there has been a long interval since the previous infusion should be monitored during the first infusion and for the first hour after the first infusion, in order to detect potential adverse signs.

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

In case of adverse reaction, either the rate of administration must be reduced or the infusion stopped. The treatment required depends on the nature and severity of the adverse reaction.

In case of shock, standard medical treatment should be implemented.

Hypersensitivity

True hypersensitivity reactions are rare. They can particularly occur in patients with anti-IgA antibodies who should be treated with particular caution. Patients with anti-IgA antibodies, in whom treatment with subcutaneous IgG products remains the only option, should be treated with SUBCUVIA only under close medical supervision.

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

Suspicion of allergic or anaphylactic type reactions requires immediate discontinuation of the injection.

Thromboembolism

Arterial and venous thromboembolic events including myocardial infarction, stroke, deep venous thrombosis and pulmonary embolism have been associated with the use of immunoglobulins. Patients should be sufficiently hydrated before use of immunoglobulins. Caution should be exercised 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.

Aseptic Meningitis Syndrome (AMS)

Aseptic meningitis syndrome has been reported to occur in association with subcutaneous immunoglobulin treatment; the symptoms usually begin within several hours to 2 days following treatment. Discontinuation of immunoglobulin treatment may result in remission of AMS within several days without sequelae.

Patients should be informed about first symptoms which encompass severe headache, neck stiffness, drowsiness, fever, photophobia, nausea, and vomiting.

Important information about some of the ingredients of Subcuvia

This medicines contains up to 98 mg (4.3 mmol) sodium per dose (bodyweight 75 kg) if the maximal daily dose (11.25 g IgG = 70 ml SUBCUVIA) is applied. This should be taken into consideration in patients on a controlled sodium diet.

Interference with serological testing

After injection of immunoglobulin the transitory rise in the various passively transferred antibodies in the patient's blood may result in misleading positive results in serological testing.

Passive transmission of antibodies to erythrocyte antigens, e.g. A, B, D may interfere with some serological tests for red cell antibodies for example the direct antiglobulin test (DAT, direct Coombs' test).

Administration of SUBCUVIA can lead to false positive readings in assays that depend on detection of beta-D-glucans for diagnosis of fungal infections; this may persist during the weeks following infusion of the product.

Transmissible agents

SUBCUVIA is made from human plasma.

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 non-enveloped viruses such as 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 viral safety.

It is strongly recommended that every time that SUBCUVIA 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.

Paediatric population

The listed warnings and precautions apply to both adults and children.

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. After administration of this product, an interval of 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.

4.6 Fertility, pregnancy and lactation

Pregnancy

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 and breast-feeding mothers. Immunoglobulin products have been shown to cross the placenta, increasingly during the third trimester. 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.

Breast-feeding

Immunoglobulins are excreted into the milk and may contribute to protecting the neonate from pathogens which have a mucosal portal of entry.

Fertility

Clinical experience with immunoglobulins suggests that no harmful effects on fertility are to be expected.

4.7 Effects on ability to drive and use machines

The ability to drive and operate machines may be impaired by some adverse reactions associated with SUBCUVIA. Patients who experience adverse reactions during treatment should wait for these to resolve before driving or operating machines.

4.8 Undesirable effects

Summary of the safety profile

Adverse reactions such as chills, headache, fever, vomiting, allergic reactions, nausea, dizziness, hyperhidrosis, pallor, paraesthesia, tachycardia, arthralgia, low blood pressure and moderate low back pain may occur occasionally.

Rarely human normal immunoglobulins may cause a sudden fall in blood pressure and, in isolated cases, anaphylactic shock, even when the patient has shown no hypersensitivity to previous administration.

Local reactions at infusion site: swelling, soreness, redness, induration, local heat, itching, bruising and rash may frequently occur.

For safety information with respect to transmissible agents, see section 4.4.

Tabulated list of adverse reactions

The table presented below is according to the MedDRA system organ classification (SOC and Preferred Term Level).

The adverse reactions presented in this section have been identified from three clinical trials and from post-marketing experience with Subcuvia.

Frequencies have been evaluated according to the following convention: Very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000), not known (cannot be estimated from the available data).

Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Frequency of Adverse Reactions (ADRs) with SUBCUVIA

MedDRA System Organ Class (SOC)	**Adverse reaction**	**Frequency**
IMMUNE SYSTEM DISORDERS	Anaphylactic shock Anaphylactic/Anaphylactoid reactions Hypersensitivity	Not known*
NERVOUS SYSTEM DISORDERS	Headache	Common
	Dizziness	Uncommon
	Tremor	Rare
	Paresthesia	Not known*
CARDIAC DISORDERS	Tachycardia	Not known*
VASCULAR DISORDERS	Peripheral coldness	Rare
	Hypotension, Hypertension Flushing, Pallor	Not known*
RESPIRATORY, THORACIC, AND MEDIASTINAL DISORDERS	Dyspnea	Not known*
GASTROINTESTINAL DISORDERS	Nausea	Uncommon
	Abdominal pain	Uncommon
	Vomiting Paresthesia oral	Not known*
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	Pruritus Erythema	Uncommon
	Urticaria	Rare
	Swelling face Rash maculo-papular Dermatitis allergic Hyperhidrosis	Not known*
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	Musculoskeletal stiffness (including Chest discomfort)	Uncommon
	Arthralgia Myalgia	Rare
	Back pain	Not known*
GENERAL DISORDERS AND	Injection site hemorrhage	Common

ADMINISTRATION SITE CONDITIONS	Injection site pain Injection site hematoma Injection site erythema Chills	
	Injection site swelling Injection site pruritus Pain Fatigue Feeling hot	Uncommon
	Injection site rash	Rare
	Pyrexia Malaise Injection site reaction Injection site urticaria Injection site induration Injection site warmth	Not known*
INVESTIGATIONS	Alanine aminotransferase increased	Rare
	Heart rate increased	Rare

* These ADRs have been reported from post marketing sources

Paediatric population

Frequency, type and severity of adverse reactions in children are the same as in adults.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; e-mail: medsafety@hpra.ie.

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: J06BA01

Human normal immunoglobulin contains mainly immunoglobulin G (IgG) with a broad spectrum of antibodies against infectious agents.

Human normal immunoglobulin contains the IgG antibodies present in the normal population. It is usually prepared from pooled plasma from not fewer than 1000 donations. It has a distribution of immunglobulin 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

Following subcutaneous administration of SUBCUVIA, peak serum levels are achieved after approximately 4 days.

Data from clinical trials show that trough levels of 7.24-7.86 g/l can be maintained by dosing regimens of 1.25 ml (0.2 g)/kg bw administered at intervals of 2 weeks. IgG and IgG-complexes are broken down in cells of the reticuloendothelial system.

With intramuscular administration, human normal immunoglobulin is bioavailable in the recipient's circulation after a delay of 2-3 days.

5.3 Preclinical safety data

Single dose toxicity studies demonstrate that the doses several times higher than the maximum recommended human dose had no toxic effects on laboratory animals.
Repeated dose toxicity testing in animals is impracticable due to interference with developing antibodies to heterologous protein.
Reproductive and developmental toxicity studies were not performed with this product.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Glycine
Sodium chloride
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

30 months.

Once opened: use immediately.

6.4 Special precautions for storage

Store in a refrigerator (2ºC - 8ºC).

During the shelf life, the product may be stored at room temperature (not more than 25ºC) for up to 6 weeks. The date of transfer to room temperature and the end of the 6-week period should be recorded on the outer carton. Once the product is stored at room temperature it must not be returned to the refrigerator and must be discarded, if not used by the end of the 6-week period.

Do not freeze.

Keep the container in the outer carton in order to protect from light.

6.5 Nature and contents of container

5 ml of solution in a vial (Type I glass) with a stopper (halogenobutyl rubber) – pack size of 1 or 20.

10 ml of solution in a vial (Type I glass) with a stopper (halogenobutyl rubber) – pack size of 1 or 20.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

The medicinal product should be brought to room or body temperature before use.

Do not use heating devices to warm up the product.

The liquid preparation is clear and pale yellow to light brown; during storage it may show formation of slight turbidity or a small amount of particulate matter.

Solutions that are cloudy or have deposits should not be used.

Entered vials must not be reused.

After opening of the vial the product must be used immediately.

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

7 MARKETING AUTHORISATION HOLDER

Baxalta Innovations GmbH
Industriestrasse 67
A-1221 Vienna
Austria

8 MARKETING AUTHORISATION NUMBER

PA2004/007/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 24 June 2005
Date of last renewal: 23 August 2008

10 DATE OF REVISION OF THE TEXT

November 2015