Package leaflet: Information for the user

SUBCUVIA 160 g/l Solution for Injection

Active substance: Human Normal Immunoglobulin

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4 .

What is in this leaflet:

1. What SUBCUVIA is and what it is used for

SUBCUVIA belongs to a class of medicines called immunoglobulins. These medicines contain antibodies which are normally found in your blood. Antibodies are proteins that help you to fight infection by neutralising bacteria, viruses, and other foreign bodies. SUBCUVIA is used in the treatment of certain diseases that are caused by a lack of antibodies in your blood. These types of diseases are called antibody deficiency syndromes. If you do not have enough antibodies, you become vulnerable to frequent infections. Regular and sufficient doses of SUBCUVIA can correct this lack of antibodies.

Adults and children can be prescribed SUBCUVIA as antibody replacement therapy. The most common reasons for people being prescribed antibody replacement therapy are:

- People who are born with an inability to make their own immune antibodies (congenital agammaglobulinaemia),
- People who cannot make enough own immune antibodies (hypogammaglobulinaemia)
- People who have a mixed group of reasons for not making enough own immune antibodies (common variable immunodeficiency)
- People whose blood and other body systems are unable to make sufficient antibodies (severe combined immunodeficiency)
- People who cannot make a particular class of antibody (IgG subclass deficiencies) with recurrent infections

In addition, SUBCUVIA is used for antibody replacement therapy with certain severe blood diseases, such as cancers of the bone marrow:

- myeloma
- chronic lymphatic leukaemia

These cancers can lead to severe secondary (acquired) antibody deficiencies and recurrent infections.

2. What you need to know before you use SUBCUVIA

Do not use SUBCUVIA

- if you are allergic (hypersensitive) to immunoglobulins or any of the other ingredients of SUBCUVIA (see Section 6 – "What SUBCUVIA contains")
- you must not inject SUBCUVIA into a blood vessel (intravascularly)
- you must not inject SUBCUVIA into a muscle (intramuscularly) if you have severe platelet deficiency (low platelets) or other blood clotting disorders.

Warning and Precautions

Talk to your doctor, pharmacist or nurse before using SUBCUVIA

The following is very important and should be considered before you receive or use SUBCUVIA:

- Infusion speed: the correct infusion speed is important (see Section 3, How to use SUBCUVIA). You are more likely to get side effects if the infusion is too fast.
- Side effects are more frequent if you
  - are using SUBCUVIA for the first time.
  - have received another immunoglobulin and have been switched to SUBCUVIA.
  - have not used SUBCUVIA treatment for more than 8 weeks.
- Immunoglobulin A (IgA) deficiency: if you suffer from a deficiency with anti-IgA antibodies. There is an increased risk of allergic reactions.
- Severe allergic reactions (anaphylaxis). You may experience severe allergic reactions with a fall in blood pressure. These reactions are rare but they can occur even if you have not previously had problems with similar treatments.
- Please tell your doctor that you have been using SUBCUVIA before you have a blood test. This is because SUBCUVIA may affect the results of the test.

<u>Home treatment</u>

Before you start home treatment you should assign a guardian person. This guardian should help you keep an eye on potential side effects. During the infusion you must look out for first signs of side effects (for further details see section 3. "How to use SUBCUVIA"). If you experience any, you or your guardian must stop the infusion immediately and contact a doctor. If you experience a severe side effect, you must seek emergency treatment immediately.

<u>Viral Safety</u>

Measures to Prevent Transmission of Infectious Agents

When medicines are made from human blood or plasma, certain measures are put in place to prevent infections being passed on to patients. These include:

- careful selection of blood and plasma donors to make sure those at risk of carrying infections are excluded,
- the testing of each donation and pools of plasma for signs of virus/infections,
- the inclusion of steps in the processing of the blood or plasma that can inactivate or remove viruses.

Despite these measures, when medicines prepared from human blood or plasma are administered, the possibility of passing on infection cannot be totally excluded. This also applies to any unknown or emerging viruses or other types of infections. The measures taken are considered effective for enveloped viruses such as human immunodeficiency virus (HIV), hepatitis B virus and hepatitis C virus, and for the non-enveloped hepatitis A and parvovirus B19 viruses. Immunoglobulins have not been associated with infections from hepatitis A and parvovirus B19 possibly because the antibodies against these infections, which are contained in the product, are protective.

It is strongly recommended that every time you receive a dose of SUBCUVIA the name and batch number of the medicine are recorded in order to maintain a record of the batches used.

Special patient groups

Your doctor will take special care if you are overweight, elderly, diabetic, or if you suffer from high blood pressure, low blood volume (hypovolaemia), or problems with your blood vessels (vascular diseases). In these conditions, immunoglobulins may increase the risk of cardiac infarction, stroke, lung embolism, or deep vein thrombosis, although only in very rare cases.

Inflammation of the layers lining the brain (aseptic meningitis, AMS)

Infusions of medicines like SUBCUVIA can occasionally result in rare inflammation of the layers lining the brain. Discontinuation of immunoglobulin treatment may result in reduction of AMS within several days. The syndrome usually begins within several hours to 2 days following immunoglobulin treatment.

Other medicines and SUBCUVIA

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. This includes medicines obtained without a prescription, or if you have received a vaccination in the last 6 weeks.

- SUBCUVIA may reduce the effect of some live virus vaccines such as measles, rubella, mumps and chicken pox. Therefore, after receiving SUBCUVIA, you may have to wait for up to 3 months before receiving certain vaccines. You may have to wait for up to 1 year after receiving SUBCUVIA before you can receive a measles vaccine.
- Do not mix SUBCUVIA with other medicinal products.

Pregnancy and breast-feeding

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

Your doctor will decide if SUBCUVIA may be used during pregnancy or breast-feeding.

If you are breast-feeding and receive SUBCUVIA, the antibodies of the medicine can also be found in the breast milk. Therefore, your baby may be protected from certain infections.

Driving and using machines

Some adverse reactions associated with SUBCUVIA may impair your ability to use and drive machines. You should wait for these reactions to resolve before using or driving machines.

3. How to use SUBCUVIA

Starting of treatment

Your treatment will be started by your doctor. At first, SUBCUVIA will be injected slowly. You will then be watched carefully for at least 20 minutes to see if you have any side effects. Once the doctor has found the right dose for you, you may be allowed to give the treatment to yourself at home.

Home treatment

Your doctor will show you how to use the syringe driver, and the infusion techniques. You doctor will also teach you how to recognize severe adverse effects and what to do if these occur. You will also be shown how to keep the treatment diary. You will be allowed to start home treatment as soon as you show that you can give yourself the treatment. You may start home treatment as long as you do not have any severe side effects.

Preparations

- Always use this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are unsure.
- Assign a guardian person who can watch you for potential side effects during the infusion and for at least 20 minutes after you received SUBCUVIA. These side effects could be a low blood pressure or allergic reaction. Your doctor will give you and your guardian detailed instructions. These include information to recognize an allergic reaction as soon as possible. Early symptoms of an allergic reaction include:
  - fall in blood pressure (hypotension)
  - increased pulse rate
  - vomiting (being sick)
  - cold sweat
  - chills
  - sensation of heat
  - hives
  - itching
  - difficulty in breathing.

  During the infusion you must look out for first signs of allergic reactions. If you experience any of the above symptoms you or your guardian must stop the infusion immediately and contact a doctor. If you have severe symptoms, you must seek emergency treatment immediately.
- You should bring the solution to room temperature (25°C) or body temperature (37°C) before use.
- Do not use heating devices to warm up the medicine.

- The solution will be 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.
- Do not reuse a vial once the stopper has been punctured.

Infusion

1. The infusion sites are the abdomen, the thighs or the buttocks. You should position the needle at an angle of 45 to 90 degrees.
2. Infuse SUBCUVIA subcutaneously (under the skin). You must make sure that SUBCUVIA is not infused into a blood vessel because this can lead to shock (See Section 2 - Take special care with SUBCUVIA).
3. Please keep strictly to the dosage and the infusion speed your doctor instructed you to use. The usual starting speed is 10 ml/h/pump. The infusion speed can be increased by 1 ml/h/pump after each new infusion up to a maximum of 20 ml/h/pump. You can use more than one pump at the same time.
4. Change the infusion site every 5-15 ml.
5. Use each syringe only once.
6. Sometimes it is not possible to give SUBCUVIA subcutaneously (under the skin). When this happens, SUBCUVIA may be given to you intramuscularly (into a muscle). Intramuscular administration must be given by your doctor or nurse.
7. Keep a full record of SUBCUVIA dosing by attaching the self-adhesive label into your dosing diary.

Disposal

Dispose of any unused product or waste material as instructed by your doctor or pharmacist. Do not put the cover back on used needles. Put used needles, syringes and vials into the puncture-proof container and keep it out of the reach and sight of children. Dispose of the full puncture-proof container as instructed by your doctor. Never put the unused needles and syringes into your household waste bin.

If you use more SUBCUVIA than you should

You should strictly keep to the dosage and infusion speed your doctor instructed you to use. Please tell your doctor if you accidentally use more SUBCUVIA than instructed.

The are no known symptoms of an overdose.

If you forget to use SUBCUVIA

Do not take a double dose to make up for a forgotten dose. Just infuse your next dose as usual and make a note in your diary that you missed a dose.

If you stop using SUBCUVIA

Tell your doctor if you decide to stop treatment and the reasons why.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist, or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

If you notice one of the following side effects, contact your doctor immediately:

- a sudden **fall in blood pressure**.
- **laboured breathing** (dyspnoea), **chest tightness**, **flushing of the face and skin**, **feeling of heat**, and **skin rash** (urticaria). These could be signs of a severe allergic reaction (anaphylactic shock and anaphylactoid reaction) and can occur even if the patient has shown no hypersensitivity to previous administration.

The following side effects may also occur during the use of SUBCUVIA:

Common side effects, occurring in 1 to 10 out of 100 treated patients:

- bleeding at the injection site (injection site haemorrhage)
- injection site pain
- bruising at the injection site (injection site haematoma)
- redness at the injection site (injection site erythema)
- chills

Uncommon side effects, occurring in 1 to 10 out of 1,000 treated patients:

- dizziness
- headache
- nausea
- itching at the injection site or generally (pruritus)
- redness of the skin (erythema)
- injection site swelling
- pain
- tiredness (fatigue)
- feeling hot
- chest discomfort

Rare side effects, occurring in 1 to 10 out of 10,000 treated patients:

- tremor
- increased heart rate (tachycardia)
- coldness in the extremities such as the hands or feet (peripheral coldness)
- pain in the stomach area (abdominal pain)
- pain in one or more joints (arthralgia)
- stiffness in the muscles and joints (musculoskeletal stiffness)
- pain in one or more muscles (myalgia)
- injection site rash
- increased levels of alanine aminotransferase
- skin rash (urticaria)

Side effects with unknown frequencies/OR: Very rare side effects, occurring in less than 1 to 10 out of 10,000 treated patients:

- allergic reactions (hypersensitivity reactions)

- sensation of prickling, tingling or creeping on the skin (paraesthesia)
- abnormally low blood presure (hypotension)
- abnormally high blood pressure (hypertension)
- flushing
- pallor
- vomiting
- swelling of the face
- rash with red spots covered with bumps (rash maculopapular)
- inflammation of the skin due to an allergy (dematitis allergic)
- excessive sweating (hyperhidrosis)
- back pain
- fever (pyrexia)
- feeling poorly (malaise)
- injection site reaction
- injection site urticaria
- hardening of the injection site (injection site induration)
- injection site warmth

Reporting of side effects

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly 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.

By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store SUBCUVIA

- Keep this medicine out of the sight and reach of children.
- Do not use this medicine after the expiry date which is stated on the label and carton after EXP. The expiry date refers to the last day of that month.
- Store at 2°C-8°C (in a refrigerator).
- Do not freeze.
- SUBCUVIA may be stored at room temperature (not more than 25°C) for up to 6 weeks. Record the date of transfer to room temperature and the end of the 6-week period on the outer carton. Once SUBCUVIA has been stored at room temperature, it must not be returned to the refrigerator. It must be discarded if not used by the end of the 6-week period.
- Keep the vial in the outer carton to protect it from light.
- Do not use this medicine if you notice the solution to appear cloudy or milky. It should be clear.
- Once a vial has been opened, the product must be used immediately.
- Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help to protect the environment.

6. Contents of the pack and other information

What SUBCUVIA contains

The active substance is human normal immunoglobulin.

It contains 16% (160 g/l) of human protein of which at least 95% is immunoglobulin G (IgG). The IgG subclass contents are:

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

The maximum IgA content is 4800 micrograms/ml.

The other ingredients are glycine, sodium chloride and water for injections.

SUBCUVIA contains about 1.4 mg sodium per ml.

What SUBCUVIA looks like and contents of the pack

SUBCUVIA is a solution for injection in a vial (0.8 g/5 ml or 1.6 g/10 ml; pack sizes of 1 vial or 20 vials). The liquid preparation is clear and pale yellow to light brown. Slight cloudiness or a small number of visible particles may form during storage. Solutions that are cloudy of have deposits should not be used.

Marketing Authorisation Holder

Baxalta Innovations GmbH
Industriestrasse 67
A-1221 Vienna
Austria
Tel: +44 (0) 1635 798 777

Manufacturer

BAXTER AG
Industriestrasse 67
A-1221 Vienna
Austria

This medicinal product is authorised in the Member States of the EEA under the following names:

SUBCUVIA

This leaflet was last approved in 11/2015

The following information is intended for medical or healthcare professionals only:

Posology and method of administration

Posology

Replacement therapy should be initiated and monitored under the supervision of a physician experienced in the treatment of immunodeficiency. Patients must be closely monitored and carefully observed for any symptoms throughout the infusion period, particularly patients starting with therapy.

The medicinal product should be administered via the subcutaneous route.

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

The dosage regimen should achieve a trough level of IgG (measured before the next infusion) of at least 5-6 g/l and aim to be within the reference interval of serum IgG for age. A loading dose of at least 0.2-0.5 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. 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.

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.

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.

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.

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

Do not use heating devices.

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

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

If well tolerated 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.

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.

Intramuscular injection must be given by a physician or by a nurse.

Incompatibilities

This medicinal product must not be mixed with other medicinal products.
