Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Hydroxocobalamin Basi 1000 microgram/mL solution for injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ampoule of 1 ml contains hydroxocobalamin chloride equivalent to 1000 microgram hydroxocobalamin.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection.
A clear, red solution, free of visible particles.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Hydroxocobalamin Basi 1000 microgram/ml solution for injection is indicated in adults, neonates and children aged 1 month to 17 years for the prophylaxis and treatment of anaemia associated with vitamin B12 deficiency. An example of vitamin B12 deficiency is Addisonian pernicious anaemia.

4.2 Posology and method of administration

Posology

The following dosage schemes are suitable for adults and children:

Addisonian pernicious anaemia and other macrocytic anaemias without neurological involvement:
Initially: 250 to 1,000 microgram intramuscularly on alternate days for one or two weeks, then 250 microgram weekly until the blood count is normal.
Maintenance: 1,000 microgram every two or three months.

Addisonian pernicious anaemia and other macrocytic anaemias, anaemia with neurological complications:
Initially: 1,000 microgram intramuscularly on alternate days as long as improvement is occurring.
Maintenance: 1,000 microgram every two months.

Prophylaxis of macrocytic anaemia associated with vitamin B12 deficiency resulting from gastrectomy, some malabsorption syndromes and strict vegetarianism:
1,000 microgram every two to three months.

Method of administration
For intramuscular administration.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Hydroxocobalamin should not be used for the treatment of megaloblastic anaemia of pregnancy unless vitamin B12 deficiency has been demonstrated.

4.4 Special warnings and precautions for use

Hydroxocobalamin administration may mask previously unrecognized folate deficiency.

The dosage schemes given above are usually satisfactory, but regular examination of the blood is advisable. If megaloblastic anaemia fails to respond to hydroxocobalamin, folate metabolism should be investigated.

Doses in excess of 10 microgram daily may produce an incomplete haematological response in patients with folate deficiency. Indiscriminate administration may mask the true diagnosis. The haematological and neurological state should be monitored regularly to ensure adequacy of therapy. Cardiac arrhythmias secondary to hypokalaemia during initial therapy have been reported. Plasma potassium should therefore be monitored during this period. Platelet count should be monitored during the first weeks of use in megaloblastic anaemia due to the possible occurrence of reactive thrombocytosis.

Interference with serological testing
Because of its dark red colour persisting for several days, hydroxocobalamin can interfere in various ways (chemical or spectral interference) with the determination of certain biological parameters, plasma or urine (*in-vitro* tests). Caution should therefore be exercised when interpreting urine or plasma colorimetric tests.
This medicinal product contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

Chloramphenicol-treated patients may respond poorly to Hydroxocobalamin Basi. Serum concentrations of hydroxocobalamin may be lowered by oral contraceptives. Antimetabolites and most antibiotics invalidate vitamin B12 assays by microbiological techniques.

4.6 Fertility, pregnancy and lactation

Pregnancy
Hydroxocobalamin should not be used for the treatment of megaloblastic anaemia of pregnancy unless vitamin B12 deficiency has been demonstrated.

Breastfeeding
Hydroxocobalamin is secreted into breast milk but this is unlikely to harm the infant, and may be beneficial if the mother and infant are vitamin B12 deficient.

4.8 Undesirable effects

Tabulated list of adverse reactions

The frequency of adverse reactions is defined using 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).

There are no modern clinical studies available that can be used to determine the frequency of undesirable effects. Therefore, all the undesirable effects listed are classed as "frequency unknown".

The following effects have been reported and are listed below by body system:

System organ class	Frequency	Undesirable effects
Blood and lymphatic system disorders	Not known	Reactive thrombocytosis can occur during the first weeks of use in megaloblastic anaemia.
Immune system disorders	Not known	Hypersensitivity reactions including skin reactions (e.g. rash, itching) and exceptionally anaphylaxis.
Nervous system disorders	Not known	Headache, sensory abnormalities such as paraesthesia, tremor.
Cardiac disorders	Not known	Arrhythmias secondary to hypokalaemia.
Gastrointestinal disorders	Not known	Nausea, vomiting, diarrhoea.
Skin and subcutaneous tissue disorders	Not known	Acneiform and bullous eruptions.
Renal and urinary disorders	Not known	Chromaturia.
General disorders and administration site conditions	Not known	Fever, chills, hot flushing, dizziness, malaise, pain. Injection site reactions including injection site pain, injection site erythema, injection site pruritus, injection site induration, and injection site swelling.

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 the HPRA Pharmacovigilance Website: www.hpra.ie.

4.9 Overdose

Treatment is unlikely to be needed in cases of overdosage.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Vitamin B12 (cyanocobalamin and analogues), hydroxocobalamin, ATC code: B03BA03.

Vitamin B12, a generic term covering both hydroxocobalamin and cyanocobalamin, plays an essential role in growth through both haematopoiesis and synthesis of cyanocobalamin, plays an essential role in growth through haematopoiesis, nucleic acid synthesis and lipid nucleic acid synthesis and lipid metabolism, especially in the nervous system (myelin synthesis). It is also involved in the activating enzyme systems of the –SH (sulfhydryl) group activating enzyme systems such as for methionine, choline and thymine.
In the gastrointestinal tract, vitamin B12 is absorbed in the ileum, in the presence of calcium, after binding to a glycoprotein secreted by the gastric mucosa called "intrinsic factor" (vitamin B12 itself is called "extrinsic factor"). In the body, vitamin B12 is metabolised into its co-enzyme form and stored in the liver, which contains about 5 mg; this amount is sufficient for biological needs for 3 to 5 years.
Vitamin B12 deficiency manifests itself as anaemia and occurs when the body's reserves are reduced to 10% of normal values. It can be caused by :
· intrinsic factor deficiency as a result of genetic predisposition (classical pernicious anaemia, Biermer anaemia), a congenital deficiency (congenital pernicious anaemia) or gastrectomy;
· disorders of vitamin B12 absorption of various etiologies;
· dietary deficiency of vitamin B12 which may occur in vegetarians or undernourished populations;
· certain situations where the need for vitamin B12 is increased, such as pregnancy or hyperthyroidism.
Vitamin B12 deficiency leads to the development of megaloblastic anaemia and demyelination, as well as other neurological changes.
Various vitamin B12 preparations can be used to treat and prevent deficiency; however, it is desirable to identify the exact cause of the deficiency before starting treatment.

5.2 Pharmacokinetic properties

After injection of hydroxocobalamin, 90% of a 100-microgram dose and 30% of a 1000-microgram dose are retained. Vitamin B12 is extensively bound to specific plasma proteins called transcobalamins; transcobalamin II appears to be involved in the rapid transport of the cobalamins to tissues. Vitamin B12 is stored in the liver, excreted in the bile, and undergoes extensive enterohepatic recycling; part of an administered dose is excreted in the urine, most of it in the first 8 hours; urinary excretion, however, accounts for only a small fraction in the reduction of total body stores acquired by dietary means. Vitamin B12 diffuses across the placenta and also appears in breast milk.

When vitamin B12 is administered orally, it is absorbed irregularly from the distal small intestine. In the stomach, free vitamin binds to intrinsic factor (FI). The vitamin B12-FI complex then moves into the small intestine where ileal receptors ingest it through phagocytosis, and vitamin fractions are absorbed. For this binding to ileal receptors, the presence of calcium and a pH greater than 5.4 is necessary; absorption is impaired in patients with absence of intrinsic factor, malabsorption syndrome, intestinal disturbances, or patients who have undergone gastrectomy. Vitamin B12 can also be absorbed independently of FI by passive diffusion in the intestinal wall, in the presence of amounts much greater than normal dietary intake (5-15 microgram).

5.3 Preclinical safety data

None stated.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride
Glacial Acetic Acid
Water for injections

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months

After first opening: Once ampoule has been opened, the product should be used immediately.

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

Glass ampoules. Pack size: 5 and 10 ampoules of 1 ml.

6.6 Special precautions for disposal

For single use only. Discard any unused contents.

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

7 MARKETING AUTHORISATION HOLDER

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