SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Hydroxocobalamin G.L. Pharma 1mg/ml solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One 1 ml ampoule contains 1.04 mg hydroxocobalamin acetate equivalent to 1 mg hydroxocobalamin (vitamin B12).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection
Red, clear solution
pH 4.3 to 4.7

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Pernicious anaemia, and other conditions with vitamin B12 deficiency where oral supplementation is not considered sufficient or else appropriate.

4.2 Posology and method of administration

Posology

- Remission therapy
  In severe acute cases of diagnosed or suspected neuropathy where rapid restoration of vitamin B12 reserves is required, 1 ampoule of Hydroxocobalamin G.L. Pharma can be administered intramuscularly or subcutaneously daily or every other day, continued for 1 to 2 weeks or until blood values are normalized.
  In severe acute cases without neuropathy, 1 ampoule is given every other day, for up to 5 times in total.

- Maintenance therapy
  Usually 1 ampoule subcutaneously or intramuscularly every 1 to 3 months

Method of administration

Intramuscular or subcutaneous use.

Duration of administration

Depending on the particular cause of the disease up to lifelong treatment may be necessary.

4.3 Contraindications

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

4.4 Special warnings and precautions for use

Hydroxocobalamin should, if possible, not be given to patients with suspected vitamin B12 deficiency

without first confirming the diagnosis.

Frequent use of vitamin B12 may mask folate deficiency. Therefore, caution should be exercised in treatment of anaemia in cases where it has not been established that this is caused by vitamin B12 deficiency.

This medicine contains less than 1 mmol sodium (23 mg) per ml, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

Chloramphenicol may antagonize the hematopoietic effect of vitamin B12. The hematopoietic effect in these patients should be monitored.

Oral contraceptives may reduce serum vitamin B12 levels.

Most antibiotics give false results of microbiological blood tests for the determination of folic acid and vitamin B12.

4.6 Fertility, pregnancy and lactation

Pregnancy
No effects during pregnancy are anticipated, since systemic exposure to hydroxocobalamin is negligible.

Breast-feeding
Hydroxocobalamin metabolites are excreted in human milk, but at therapeutic doses of Hydroxocobalamin G.L. Pharma no effects on the breastfed newborns/infants are anticipated.

Fertility
No known risks.

4.7 Effects on ability to drive and use machines

Hydroxocobalamin G.L. Pharma has no known effects on the ability to drive and use machines.

4.8 Undesirable effects

The frequencies are defined as follows: 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), and not known (cannot be estimated from available data).

System organ class	Frequency	Adverse event
Immune system disorders	not known	Allergic hypersensitivity reactions, including skin reactions, bronchospasm, oedema, angioedema, anaphylaxis.
Nervous system disorders	not known	Tremor Headache Paraesthesia
Cardiac disorders	not known	Arrhythmias (secondary to hypokalaemia)
Gastrointestinal disorders	not known	Diarrhoea Nausea Vomiting

System organ class	Frequency	Adverse event
Skin and subcutaneous tissue disorders	not known	Acneiform dermatitis Bullous eruption
	not known	Erythema Urticaria Pruritus Rash Itching
Renal and urinary disorders	not known	Chromaturia Oxalate nephropathy
General disorders and administration site conditions	not known	Local injection site reaction such as induration, pain, swelling, or necrosis. Fever Chills Hot flushing Dizziness Malaise

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 national reporting system listed in Appendix V.

4.9 Overdose

The substance is of low acute toxicity. Overdose generally causes no symptoms and symptomatic treatment should only be required in exceptional cases.

Symptoms
No symptoms of overdosing are established.

Treatment
Symptomatic treatment only in exceptional circumstances.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Vitamin B12 is essential in humans and is a part of two important enzyme reactions.
In the first one deoxyadenosylcobalamin is a co-factor for the conversion of methylmalonyl-CoA to succinyl-CoA via the enzyme methylmalonyl-Coa mutas. In the event of B12 deficiency, this conversion cannot take place and the substrate methylmalonyl-CoA accumulates, resulting in the accumulation of the metabolite methylmalonic acid and to synthesizing of abnormal fatty acids which are accumulated in the cell membranes including in the CNS.

The second reaction requires methylcobalamin when 5-methyl-tetrahydrofolate is converted to tetrahydrofolate and homocysteine to methionine by the enzyme methionine synthetase (5-methyl-tetrahydrofolate homocysteine methyltransferase). In the event of B12 deficiency, 5-methyltetrahydrofolate (the “methyl folate trap”) and homocysteine accumulates. This leads to a deficiency of folate co-factors necessary for DNA syntheses. The determination of methylmalonic acid and homocysteine can be used when investigating and diagnosing vitamin B12 and folic acid

deficiency. Vitamin B12 has been shown to normalize elevated methylmalonic acid levels. Studies have also shown that vitamin B12 in combination with folic acid normalizes elevated homocysteine levels. Increased homocysteine levels have been shown to be one of many independent risk factors for, among other things cardiovascular disease.

5.2 Pharmacokinetic properties

Absorption
Following parenteral administration of hydroxocobalamin, plasma levels are rapidly reached. Following intramuscular injections, Vitamin B_{12} reaches the highest levels within the first hour. In healthy individuals and in vitamin B_{12}-deficient patients, IM administration of hydroxocobalamin produces a more sustained rise in serum cobalamin concentration and less short-term urinary excretion of cobalamin than does a similar dose of cyanocobalamin. In addition, hydroxocobalamin is absorbed more slowly from the site of injection than cyanocobalamin.
Following IM administration, the C_{max} of hydroxocobalamin is estimated at 22-72 nmol/L and the T_{max} at 60-480 minutes. The great storage and long biological half-life (350-400 days in humans) of the vitamin provide substantial protection against periods of deprivation. There is no available data on relative bioavailability between intramuscular and subcutaneous administration routes.

Distribution
Vitamin B12 is extensively bound to specific plasma proteins called transcobalamins. Vitamin B_{12} is distributed into the liver, bone marrow, and other tissues, including the placenta. In addition, this compound has been found in the cerebrospinal fluid with concentrations correlated with those in serum. Vitamin B_{12} is distributed into the milk of nursing women in concentrations that approximate the maternal blood vitamin B_{12} concentration. Total body stores of vitamin B_{12} in healthy individuals are estimated to range from 1–11 mg, with an average of 5 mg; 50–90% is stored in the liver. Vitamin B_{12} is believed to be converted to coenzyme form in the liver and is probably stored in tissues in this form.

Metabolism
When vitamin B12 is released from transcobalamin, it is converted to coenzyme forms which then link to the two cobalamin-dependent enzymes; methionine synthetase and methylmalonyl-CoA mutase and are converted in the cell fluid to methylcobalamin or in the mitochondria to 5´-deoxyadenosylcobalamin.
Methylcobalamin is a small part of intracellular vitamin B12. Methylcobalamin is the main form of vitamin B12 in the plasma and the form that is reduced in vitamin B12 deficiency.

Elimination
Vitamin B12 is stored in the liver, excreted via the bile and undergoes extensive entero-hepatic recycling. Within 72 hours after IM injection of 0.5–1 mg of hydroxocobalamin, 16–66% of the dose may be excreted in urine. Renal excretion of parenterally administered vitamin increases with higher doses. Following intramuscular administration, a maximum of approximately 50% of the normal stores of vitamin B12 is retained. No difference could be detected in the amount of B_{12} excreted following the injection of 1.5 µg of the labelled vitamin by subjects with normal serum B_{12} and those with vitamin deficiency.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction and development.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium acetate trihydrate(for pH adjustment)
Acetic acid, glacial (for pH adjustment)
Sodium chloride
Water for injection

6.2 Incompatibilities

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

6.3 Shelf life

30 months

6.4 Special precautions for storage

Do not store above 30°C. Do not freeze.

6.5 Nature and contents of container

Clear glass ampoules marked with two coloured rings, 3 x 1 ml and 5 x 1 ml.

6.6 Special precautions for disposal and other handling

How the ampoule is opened:
1. Localise the OPC (one-point-cut), which is marked on the top section of the ampoule with a coloured dot, and let it point upward.
2. Make sure to remove all the liquid from the top of the ampoule by gently tapping it.
3. Put the other hand on the top of the ampoule with your thumb on the point.
4. Break the neck of the ampoule in the direction away from you.

7. MARKETING AUTHORISATION HOLDER

[To be completed nationally]

8. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT

2023-06-29