New Zealand Data Sheet

1 PRODUCT NAME

HYDROXOCOBALAMIN PANPHARMA Solution for injection 1 mg/mL

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Hydroxocobalamin acetate 1 mg/mL

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Addisonian pernicious anaemia. Prophylaxis and treatment of other macrocytic anaemias associated with vitamin B12 deficiency. Tobacco amblyopia and Leber's optic atrophy.

4.2 Dose and method of administration

HYDROXOCOBALAMIN PANPHARMA injection is to be administered intramuscularly.

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 micrograms intramuscularly on alternate days for one to two weeks, then 250 micrograms weekly until the blood count is normal.

Maintenance: 1,000 micrograms every two or three months.

Addisonian pernicious anaemia and other macrocytic anaemias with neurological involvement.

Initially: 1,000 micrograms on alternate days as long as improvement is occurring.
Maintenance: 1,000 micrograms every two months.
Prophylaxis of macrocytic anaemia associated with vitamin B_{12} deficiency resulting from gastrectomy, some malabsorption syndromes and strict vegetarianism.
1,000 micrograms every two or three months.

Tobacco amblyopia and Leber's optic atrophy.

Initially: 1,000 micrograms or more daily by intramuscular injection for two weeks then twice weekly as long as improvement is occurring.

Maintenance: 1,000 micrograms monthly.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
Known sensitivity to cobalt.
HYDROXOCOBALAMIN PANPHARMA should not be used for the treatment of megaloblastic anaemia in pregnancy (see 4.4 Special warnings and precautions for use; 4.6 Fertility, pregnancy and lactation).

4.4 Special warnings and precautions for use

DO NOT USE INTRAVENOUSLY.

A sensitivity history should be obtained from the patient prior to administration of vitamin B_{12}. An intradermal test dose is recommended before vitamin B_{12} is administered to patients who may be sensitive to cobalamins.

Hypokalaemia and cardiac arrest have been reported when megaloblastic anaemia is treated intensively.

Serum potassium is to be carefully monitored during the initial phase of treatment in pernicious anaemia.

Hydroxocobalamin should only be used in properly diagnosed cases of deficiency. Do not use hydroxocobalamin until diagnosis is fully established, as it may mask symptoms of subacute degeneration of the spinal cord, or of the true diagnosis of pernicious anaemia. Folic acid may potentiate the neurological complications of vitamin B_{12} deficiency, so should not be administered to patients with pernicious anaemia (see 4.5 Interaction with other medicines and other forms of interaction).

The platelet count should be monitored during the first weeks of treatment of megaloblastic anaemia because of the possibility of reactive thrombocytosis. Long-term parenteral administration can increase the risk of aluminium toxicity in patients with renal impairment and in preterm infants.

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

HYDROXOCOBALAMIN PANPHARMA, folate metabolism should be investigated. Doses in excess of 10 micrograms daily may produce a haematological response in patients with folate deficiency. Indiscriminate administration may mask the true diagnosis.

Before commencing treatment of pernicious anaemia it is important to establish baseline levels for haematological parameters and plasma levels of cobalamin and to monitor response at frequent intervals particularly in the first few weeks of treatment and thereafter at less frequent intervals.

Cardiac arrhythmias secondary to hypokalaemia during initial therapy have been reported. Plasma potassium should therefore be monitored during this period.

The therapeutic response to hydroxocobalamin may be impaired by concurrent infection, uraemia, folic acid or iron deficiency.

Treatment with hydroxocobalamin may unmask polycythaemia vera, because vitamin B_{12} deficiency may suppress the symptoms of this condition.

The administration of hydroxocobalamin may impart a pink, red/reddish colour to blood, urine, body fluids and discoloured faeces.

Most antibiotics, methotrexate and pyrimethane invalidate folic acid and vitamin B_{12} microbiological blood analysis. The administration of hydroxocobalamin may affect blood homocysteine levels.

The administration of hydroxocobalamin may affect various clinical chemistry laboratory tests due to its characteristic of absorbing light. The chief laboratory tests that may be affected by the administration of hydroxocobalamin are those that involve the use of colorimetric methods or that require the use of Nicotinamide Adenine Dinucleotide (NAD) and Nicotinamide Adenine Dinucleotide Phosphate (NADP).

An artifactual increase has been observed in the levels of creatinine, bilirubin, triglycerides, cholesterol, total proteins, glucose, albumin and alkaline phosphatase and a decrease in alanine aminotransferase (ALT) and amylase. Unpredictable results have been observed in the levels of phosphatase, uric acid, aspartate aminotransferase (AST), creatine phosphokinase (CPK), creatine phosphokinase isoenzymes (CK-MB) and lactate dehydrogenase (LDH). The effects on the various laboratory tests are summarised in the following table:

Laboratory parameters	**No Interference**	**Artificially increased**	**Artificially decreased**	**Unpredictable results**
Clinical chemistry	Calcium Sodium Potassium Chlorine Urea Gamma-GT	Creatinine Bilirubin Tiglycerides Cholesterol Total proteins Glucose Albumin	ALT Amylase	Phosphates Uric acid AST CPK CK-MB LDH

		Alkaline Phosphatase		
Haematology	Erythrocytes Haematocrit MCV Leucocytes Lymphocytes Monocytes Eosinophils Neutrophils Platelets	Haemoglobin MCH MCHC Basophils		
Coagulation				aPTT, PT (Quick or INR)
Urinalysis	pH Glucose Proteins Erythrocytes Leucocytes Ketones Bilirubin Urobilinogen Nitrites			

4.5 Interaction with other medicines and other forms of interaction

Chloramphenicol-treated patients may respond poorly to hydroxocobalamin. The haematological response should be carefully monitored in patients receiving both these medicines.

Hydroxocobalamin may antagonise the toxic effects of cyanide poisoning.

Serum concentrations of hydroxocobalamin may be lowered by oral contraceptives. The clinical relevance of these interactions is not known, but they should be taken into consideration when measuring plasma vitamin B12 concentrations.

Vitamin B12 concentrations in the blood may be reduced following administration of large and continuous doses of folic acid. Folic acid administration may impair the therapeutic response to hydroxocobalamin.

4.6 Fertility, pregnancy and lactation

Pregnancy

Problems in humans have not been documented with intake of normal daily amounts. Vitamin B_{12} crosses the placental barrier. There are no studies establishing the safety of this medicine during pregnancy. It is not recommended for pregnancy unless the expected benefits outweigh any potential risk to the infant.

Megaloblastic anaemia occurring during pregnancy is usually due to folic acid deficiency rather than vitamin B_{12} deficiency. Hydroxocobalamin should not be used for the treatment of megaloblastic anaemia in pregnancy caused by folic acid deficiency.

Breastfeeding

Hydroxocobalamin is distributed into breast milk. Therefore, it is not recommended for breastfeeding mothers unless the expected benefits to the mother outweigh any potential risk to the infant.

Fertility

No information held by the sponsor.

4.7 Effects on ability to drive and use machines

Not relevant.

4.8 Undesirable effects

Typical adverse events include transitory hypertension, hypokalaemia at the start of the treatment and loss of pigmentation of the skin and mucosa. All these skin reactions tend typically to regress after 1 or 2 days.

Sensitisation to hydroxocobalamin is rare but may manifest itself as itching exanthema, chills, fever, hot flushes, nausea, dizziness, and exceptionally, anaphylaxis. Acneiform and bullous eruptions have been reported rarely.

Antibodies to hydroxocobalamin-transcobalamin II complex may develop during hydroxocobalamin therapy.

Other reported adverse effects include diarrhoea, faeces may have a reddish colour, urine may take on a pink or reddish tinge, nausea, vomiting, headache, dizziness, peripheral vascular thrombosis, chest pain/discomfort, cardiac arrest, injection site reactions, allergic reactions, generalised itching, redding of the skin, bronchospasm, dysnoea, sensation of heat and cold, malaise, urticaria or a feeling of swelling of the whole body, angioedema, orpharyngeal oedema, cardiocirculatory collapse, eczematous skin lesions, acne and folliculitis.

Exceptionally anaphylactic shock has been reported.

Pulmonary oedema and congestive heart failure have been reported during early vitamin B12 treatment, possibly as a result of an increase in blood volume induced by the medicine.

Polycythaemia vera may occur (see 4.4 Special warnings and precautions for use).

Arrhythmias secondary to hypokalaemia have appeared at the beginning of parenteral treatment with hydroxocobalamin.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/reporting/

4.9 Overdose

Treatment is unlikely to be needed in cases of overdosage.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antianaemic preparations – Vitamin B12.
ATC code: B03BA03

Hydroxocobalamin may be regarded as a precursor of two co-enzymes, which are involved in various biological systems in man. Co-enzyme B12 is required for the conversion of methylmalonate to succinate. Deficiency of this enzyme could therefore interfere with the production of lipoprotein in myelin sheath tissue and so give rise neurological lesions. Methylcobalamin is necessary for the conversion of homocysteine to methionine, which is essential for the metabolism of folic acid. Deficiency of tetrahydrafolate leads to reduced synthesis of thymidylate resulting in reduced synthesis of DNA, which is essential for cell maturation. Vitamin B12 is also concerned in the maintenance of sulphydryl groups in reduced form, deficiency leading to decreased amounts of reduced SH content of erythrocytes and liver cells.

5.2 Pharmacokinetic properties

An intramuscular injection of hydroxocobalamin produces higher serum levels than the same dose of cyanocobalamin, and these levels are well maintained.

Vitamin B_{12} exists in four major forms referred to collectively as cobalamins; deoxyadenosylcobalamin, methylcobalamin, hydroxocobalamin, and cyanocobalamin. Cobalamins are absorbed in the ileum and stored in the liver. They continuously undergo enterohepatic recycling via secretion in the bile. Part of a dose is excreted in the urine, most of it in the first 8 hours. As many as five different forms of cobalamin have been identified in the urine. The proportion of the dose excreted in the urine increases with the size of the dose, rising from 8% of 100 microgram dose to 29% of a 1,000 microgram dose. In a normal person, following injection of hydroxocobalamin, the half-life in the serum depends on the glomerular filtration rate, whereas in a patient with deficient stores the removal from the plasma will depend on the rate of absorption into the body stores as well as the renal excretion.

Cobalamins are extensively bound to two specific plasma proteins called transcobalamin 1 and 2; 70% to transcobalamin 1, 5% to transcobalamin 2. The normal average blood level of vitamin B_{12} is 472 pg/mL. Range is 163-925 pg/mL. A vitamin B_{12} below 160 pg/mL indicates a deficiency state.

Cobalamins diffuse across the placenta. No information has been found regarding the effect of age, renal hepatic dysfunction on the kinetics of hydroxocobalamin.

During therapy with weekly intramuscular doses of 500 mcg, serum vitamin B_{12} concentration of over 0.8 ng/mL are attained in 2 weeks and of 5 ng/mL in 8 weeks, rising in some cases to 15 ng/mL.

5.3 Preclinical safety data

Not applicable

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

sodium chloride
sodium acetate
acetic acid
water for injections

As single dose ampoules, no preservatives are required.

6.2 Incompatibilities

The administration of hydroxocobalamin is incompatible with concomitant infusion of diazepam, dobutamine, dopamine, fentanyl, nitroglycerin, propofol and thiopental.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Store below 25°C. Protect from light.
Any portion of the contents remaining should be discarded.

6.5 Nature and contents of container

Ampoules of 1 mL containing a clear, red solution containing 1 mg (1,000 micrograms) hydroxocobalamin acetate per mL equivalent to 0.96 mg hydroxocobalamin per mL.

Ampoules of 1 mL in boxes of 3.

6.6 Special precautions for disposal

No special requirements for disposal.

7 MEDICINE SCHEDULE

General Sales Medicine

8 SPONSOR

BNM Group
39 Anzac Road
Browns Bay
Auckland 0753

Phone 0800 565 633

9 DATE OF FIRST APPROVAL

Date of publication in the New Zealand Gazette of consent to distribute the medicine: 31 May 2007

10 DATE OF REVISION OF TEXT

02 March 2022

Summary table of changes

Section changed	Summary of new information
4.4	Addition of the following information: • platelet count should be monitored in first weeks of treatment of megaloblastic anaemia. • long-term parenteral administration can increase risk of aluminium toxicity in patients in renal impairment and in pre-term infants. • warning hydroxocobalamin may impart, pink, red/reddish colour to blood urine, body fluids and discoloured faeces. • addition of information on various laboratory parameters. Relocation of information relating to antibiotics from section 4.5.

4.5	Addition of advice that consideration need to be taken in measuring plasma vitamin B12 concentration in interactions with oral contraceptives. Deletion of repetitive text following addition of text from innovator datasheet. Addition of information relating to cyanide interaction.
4.8	Addition of following adverse effects: transitory hypertension; hypokalemia; loss of pigmentation of the skin and mucosa; reddish colour faeces; urine may turn a pink or reddish tinge; allergic reactions; generalised itching; redding of the skin; bronchospasm; dysnoea; angioedema; orpharyngeal oedema; cardiocirculatory collapse; anaphylactic shock
4.9	Addition for overdose information as per the Datasheet template.
6.2	Addition of precautionary statement relating to lack of compatibility with diazepam, dobutamine, dopamine, fentanyl, nitroglycerin, propofol and thiopental.