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 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 B_{12} 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 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.

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.

Serum concentrations of hydroxocobalamin may be lowered by oral contraceptives.

These interactions are unlikely to have clinical significance.

Vitamin B_{12} 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.

Most antibiotics, methotrexate and pyrimethane invalidate folic acid and vitamin B_{12} microbiological blood analysis.

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 operate machines

Not relevant.

4.8 Undesirable effects

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, nausea, vomiting, headache, dizziness, peripheral vascular thrombosis, chest pain/discomfort, cardiac arrest, injection site reactions, sensation of heat and cold, malaise, urticaria or a feeling of swelling of the whole body, eczematous skin lesions, acne and folliculitis.

Pulmonary oedema and congestive heart failure have been reported during early vitamin B_{12} 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.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antianaemic preparations – Vitamin B_{12}.
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 B_{12} 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 B_{12} 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

Not applicable.

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

Distributor:

ABM Pharma Ltd
39 Anzac Road
Browns Bay
Auckland 0753

Ph: 0800 437 849

Manufacturer*:*

Rotexmedica GmbH
Bunsenstrasse 4
22946 Trittau
Germany

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

10 January 2018

Summary table of changes

SECTION CHANGED	SUMMARY OF NEW INFORMATION
4.3	Contraindications: - "Known sensitivity to cobalt." was included - A statement from section "Use in pregnancy" was moved to this section
4.4	Special warnings and precautions for use: a warning about Hypokalaemia and cardiac arrest was included
4.5	Interaction with other medicines and other forms of interaction was updated
4.6	Fertility, pregnancy and lactation was updated
8	The manufacturer's details were reinstated