AUSTRALIAN PRODUCT INFORMATION – NEO-B12 INJECTION (Hydroxocobalamin chloride)

1. NAME OF THE MEDICINE

Hydroxocobalamin chloride (vitamin B_{12})

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ampoule contains hydroxocobalamin chloride equivalent to hydroxocobalamin 1000 micrograms, sodium chloride 9.0 milligrams and 1N acetic acid for pH adjustment and Water for Injections. The pH of the solution is approximately 4.6.

Hydroxocobalamin is a dark red, odourless crystalline powder or crystals. It is soluble in water and alcohol, sparingly soluble in methyl alcohol and practically insoluble in acetone, chloroform and ether.

For the full list of excipients, see Section 6.1 List of excipients.

3. PHARMACEUTICAL FORM

Neo-B12 Injection is a clear, dark red, sterile solution for injection supplied in colourless glass containers (ampoules) of 1 mL.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

Prophylaxis and treatment of pernicious (Addisonian) anaemia and other macrocytic anaemias associated with vitamin B_{12} deficiency. Treatment of optic neuropathies such as tobacco amblyopia and Leber's optic atrophy.

4.2 Dose and Method of Administration

Dosage

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 for one to two weeks.

Maintenance: 1,000 micrograms every two months.

Prophylaxis of macrocytic anaemia associated with vitamin B_{12} deficiency resulting from gastrectomy, some malabsorption syndromes and nutritional deficiencies:

1,000 micrograms every two or three months.

Tobacco amblyopia and Leber's optic atrophy:

Initially: 1,000 micrograms daily by intramuscular injection for two weeks then twice weekly for four weeks.

Maintenance: 1,000 micrograms monthly.

Method of Administration

Neo-B12 Injection is to be administered intramuscularly.

This product contains no antimicrobial agent. It is for single use in one patient only. Discard any residue.

4.3 Contraindications

Known sensitivity to hydroxocobalamin, or any other ingredient in Neo-B12 Injection. Known sensitivity to cobalt.

Hydroxocobalamin should not be used for the treatment of megaloblastic anaemia of pregnancy (see Section 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.

Diagnosis of vitamin B_{12} deficiency should be confirmed by laboratory investigation before institution of hydroxocobalamin (vitamin B_{12}) therapy. 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 Section 4.5 Interactions with other medicines and other forms of interactions).

Regular blood tests to determine vitamin B_{12} levels are advisable during treatment.

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.

Administration of hydroxocobalamin doses in excess of 10 micrograms daily may improve folate deficient megaloblastic anaemia, and obscure the true diagnosis.

The therapeutic response to hydroxocobalamin may be impaired by concurrent infection, uraemia, folic acid or iron deficiency, or by drugs with bone marrow suppressing effects, such as chloramphenicol (see Section 4.5 Interactions with other medicines and other forms of interactions).

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.

Use in the elderly

No data available.

Paediatric use

No data available.

Effects on laboratory tests

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

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	Creatinine Bilirubin Tiglycerides	ALT Amylase	Phosphates Uric acid AST

	Chlorine Urea Gamma-GT	Cholesterol Total proteins Glucose Albumin Alkaline Phosphatase	CPK CK-MB LDH
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 Interactions with Other Medicines and Other Forms of Interactions

Concurrent administration of chloramphenicol and hydroxocobalamin may impair the therapeutic response to hydroxocobalamin in vitamin B_{12} deficient patients. The haematological response should be carefully monitored in patients receiving both these drugs.

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 B_{12} concentrations.

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.

4.6 Fertility, Pregnancy and Lactation

Effects on fertility

No data available.

Use in 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 drug 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 of pregnancy caused by folic acid deficiency.

Use in lactation

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.

4.7 Effects on Ability to Drive and Use Machines

The effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration.

4.8 Adverse Effects (Undesirable Effects)

Sensitisation to hydroxocobalamin is rare, but may manifest itself as itching exanthema and rarely, anaphylaxis.

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

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.

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, oropharyngeal 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 B_{12} treatment, possibly as a result of an increase in blood volume induced by the drug.

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

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

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration 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 at www.tga.gov.au/reporting-problems.

4.9 Overdose

No data available.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Mechanism of action

Several chemically related forms of vitamin B_{12}, differing in slight modification of a side chain attached to the cobalamin nucleus have been isolated. Two such variants of vitamin B_{12} are cyanocobalamin and hydroxocobalamin.

Vitamin B_{12} is essential for normal growth, haematopoiesis, production of all epithelial cells and maintenance of myelin throughout the nervous system. Whenever nucleic acid synthesis occurs and therefore whenever cell reproduction occurs, vitamin B_{12} is required.

The amounts of vitamin B_{12} needed to maintain normal blood forming functions are small and low doses are sufficient to correct the usual symptoms of vitamin B_{12} deficiency.

Vitamin B_{12} acts as an enzyme or co-enzyme in a number of metabolic processes and is transformed in the body to at least two compounds which possess enzymatic properties.

i) Co-enzyme B_{12} is required for conversion of propionate to succinate, thus involving vitamin B_{12} in both fat and carbohydrate metabolism.

ii) Methylcobalamin acts in a transmethylation process converting homocysteine to methionine, thus involving vitamin B_{12} in fat and protein metabolism.

In some cases of vitamin B_{12} deficiency, severe neurological symptoms develop, as vitamin B_{12} is necessary for the formation of protein structures required for the integrity of the nerve cell and myelin sheath.

Clinical trials

No data available

5.2 Pharmacokinetic Properties

Hydroxocobalamin produces higher and more prolonged serum levels of vitamin B_{12} than cyanocobalamin when given by intramuscular injection in the same dosage. Hydroxocobalamin disperses more slowly from the site of injection than cyanocobalamin, is more strongly bound to plasma proteins and accumulates in the liver to a greater extent.

Hydroxocobalamin is excreted in the bile and urine, but more slowly than cyanocobalamin. Hydroxocobalamin combines with cyanide and thus acts as a cyanide antagonist *in vivo* resulting in the formation of cyanocobalamin.

5.3 Preclinical Safety Data

Genotoxicity

No data available.

Carcinogenicity

No data available.

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

Acetic acid

Sodium chloride

Water for injections

6.2 Incompatibilities

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 Shelf life

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 Special Precautions for Storage

Neo-B12 Injection should be stored below 25°C.

6.5 Nature and Contents of Container

Type I clear glass ampoules containing 1 mg/ mL (1,000 micrograms/ mL).

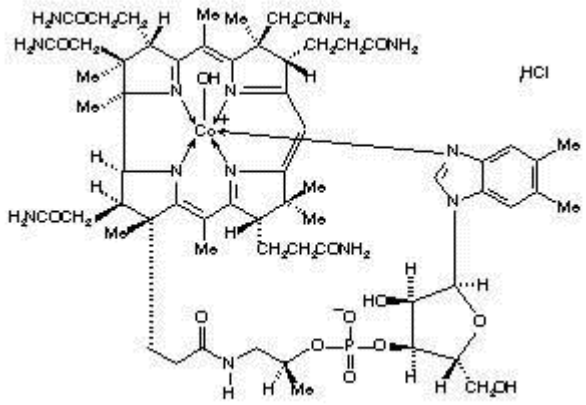
3 x 1 mL ampoules

6.6 Special Precautions for Disposal

In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements.

6.7 Physicochemical Properties

Chemical structure



Molecular formula: C62H90ClCoN13O15P. Molecular weight: 1383.

CAS number

58288-50-9.

7. MEDICINE SCHEDULE (POISONS STANDARD)

Not Scheduled

8. SPONSOR

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9. DATE OF FIRST APPROVAL

25 September 2006

10. DATE OF REVISION

4 November 2022

Summary Table of Changes

Section changed	Summary of new information
All	Minor formatting changes for consistency.
6.2	Deleted information not relevant to the Neo-B12 product information as it describes incompatibilities to infusions, whereas Neo-B12 is an intramuscular injection.