NEW ZEALAND DATA SHEET

1. PRODUCT NAME

Neo-B12 Injection Hydroxocobalamin 1000 microgram/1 mL

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each Neo-B12 Injection ampoule contains hydroxocobalamin chloride equivalent to hydroxocobalamin anhydrous 1000 micrograms sodium chloride 9.0 milligrams and 1N acetic acid for pH adjustment and Water for Injections.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection

Neo-B12 Injection is a clear, dark red coloured sterile solution, free from visible particles supplied in colourless glass ampoules of 1 mL.

The pH of the solution is approximately 4.6.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Neo-B12 Injection is indicated for: the 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

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

Neo-B12 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 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.

4.3 Contraindications

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

Known sensitivity to cobalt.

Neo-B12 Injection should not be used for the treatment of megaloblastic anaemia of pregnancy (see section 4.6)

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).

Regular blood tests to determine vitamin B12 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).

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 Alkaline Phosphatase	ALT Amylase	Phosphates Uric acid AST CPK CK-MB LDH
Haematology	Erythrocytes Haematocrit MCV Leucocytes Lymphocytes Monocytes Eosinophils Neutrophils	Haemoglobin MCH MCHC Basophils		

	Platelets	
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

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 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

Fertility

No data available.

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.

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 machinery

No data available.

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 and rarely, anaphylaxis.

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

Polycythaemia vera may occur (see section 4.4).

Arrhythmias secondary to hypokalaemia have appeared at the beginning of parenteraltreatment 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 overdose.

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

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, and 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.

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 accumulated 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.

Reproductive and developmental toxicity

No data available.

6. PHARMACEUTICAL PARTICUALRS

6.1 List of excipients

- Acetic acid
- Sodium chloride
- Water for injections

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

2 years

6.4 Special precautions for storage

Store below 25ºC

6.5 Nature and contents of container

Boxes of 3 x 1 mL clear glass ampoules

6.6 Special precautions for disposal

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

7. MEDICINE SCHEDULE

General Sale Medicine

8. SPONSOR

Pfizer New Zealand Limited

P O Box 3998

Auckland, New Zealand, 1140

Toll Free Number: 0800 736 363

9. DATE OF FIRST APPROVAL

26 Oct 2006

10. DATE OF REVISION OF THE TEXT

15 October 2021

Summary table of changes

Section changed	Summary of new information
All	Deletion of ™ superscript throughout.
4.4	Information added: • platelet count should be monitored in first weeks of treatment of megaloblastic anaemia. • long-term parenteral administration can increase risk of aluminum 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 antibotics.
4.5	Information on: • hydroxocobalamin may antagonise the toxic effects of cyanide poisoning • advice that consideration need to be taken in measuring plasma vitamin B12 concentration in interactions with oral contraceptives.
4.8	The following adverse effects are added: transitory hypertension; hypokalaemia; 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
6.2	Addition of precautionary statement relating to lack of compatibility with diazepam, dobutamine, dopamine, fentanyl, nitroglycerin, propofol and thiopental.