PT Eisai Indonesia
Bogor Factory

Brochure/ Insertion Design of Methycobal Injection 1 ml X 10 Ampules

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A Drug for Peripheral Neuropathies

Methycobal® 500 μg

INJECTION

Mecobalamin

Methycobal is a mecobalamin preparation which Eisai Co., Ltd. has developed, through original technology, as a drug for peripheral neuropathies.
Biochemically, mecobalamin is a B_{12} - containing coenzyme with an active methyl base. It participates in transmethylation reactions and is the most active of all B_{12} homologs in the body with respect to nucleid acid, protein, and lipid metabolism. Methycobal acts to repair damaged nerve tissue in nerve disorders such as axonal degeneration and demyelination; and, it is involved in erythroblast maturation, promotion of erythroblast division, and heme synthesis, thus acting to improve the status of the blood in megaloblastic anemia. Methycobal is the first preparation with which it has been documented, by double-blind clinical trials, that mecobalamin is effective not only on megaloblastic anemia but also on peripheral neuropathies such as diabetic neurological disorders and multiple neuritis.

Composition

Each (1.0 ml) ampule contains 500 μg of mecobalamin.

Indications

Peripheral neuropathies.

Dosage and Administration

The usual adult dose is 1 ampule, equivalent to 500 μg of mecobalamin administered intramuscularly or intravenously three times a week.
The dose should be adjusted according to the age of patient and severity of symptoms.

Drug interactions

It is not known whether Methycobal Injection can cause clinically significant interactions with other drugs.

Adverse Reactions

1) Hypersensitivity
   Use of the drug should be discontinued if symptoms of hypersensitivity, such as eruptions occur.
2) Other
   Infrequently, pain and induration at the site of injection and headache, sweating or fever may rarely occur.

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Precautions in Handling

1) Because Methycobal is susceptible to photolysis, Methycobal ampules are packed in LPE (Light - Protect - Easy Open) to prevent from the light just before use. Methycobal Injection must be use promptly after the package is opened, and care must be taken not expose the ampules to direct light.
2) In intramuscular administration, care should be exercised, as suggested below, to avoid adverse effects on tissues or nerves.
   a) Repeated injection at the same site should be avoided. Particular care should be exercised when administering this drugs to neonates, premature infants, infants and children.
   b) The course of nerves should be avoided for the site of injection.
   c) If the patient complains of pain or if blood reflux occurs when the syringe needle is stuck, withdraw it immediately and try at a different site.
3) The Methycobal injection is a one-point-cut type ampule. It is recommended that the cut point of the ampule be wiped clean with an alcohol swab.
4) This drug should not be used over a period of months if there is lack of satisfactory clinical response in patients with megaloblastic anemia or with peripheral neuropathies probably due to vitamin B_{12} deficiency.

Contraindications

Patients known hypersensitivity to this drug.

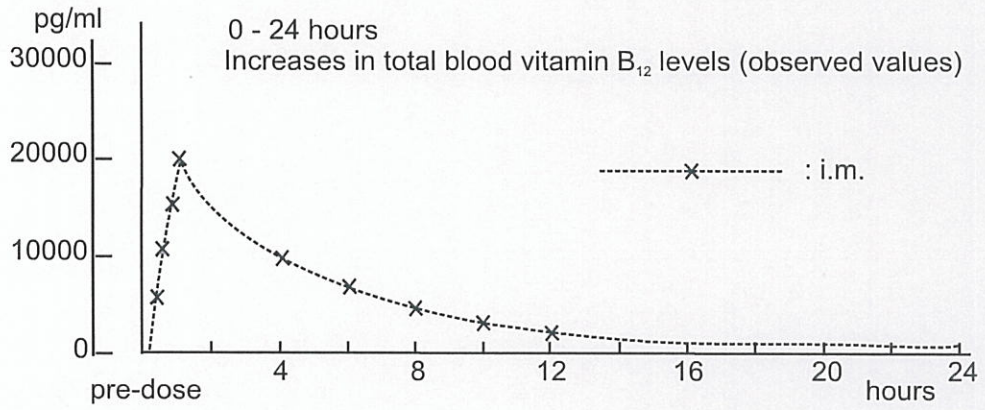
Pharmacodynamics

1. Mecobalamin promotes the metabolism of nucleic acids, proteins and lipids.
   In an experiment using brain-derived cell strains obtained from albino rats, mecobalamin acted as a coenzyme in methionine synthesis. In particular, it was found to be involved in the synthesis of thymidine from deoxyuridine and to accelerate the synthesis of DNA and RNA. In another experiments using glia cells, mecobalamin was found to accelerate the synthesis of lecithin, a major component of the myelin sheath.[1).2).]
2. Mecobalamin is efficiently transferred to nerve tissues and improves metabolic disorders.
   Mecobalamin is a CH_3 - vitamin B_{12} which is found in high concentrations in blood and cerebrospinal fluid. In an experiment in rats, it was transferred to nerve cell organelles more efficiently than CN-vitamin B_{12}. It also accelerated the synthesis of the major structural component of the axon (protein) in sciatic nerve cells of rats with experimental diabetes and returned the protein transport rate close to normal, resulting in the maintenance of axonal function.[3).4).]
3. Mecobalamin repairs nerve tissues in experimental nerve injury models.
   In experiments conducted in rats and rabbits, mecobalamin was neuropathologically and electrophysiologically shown to inhibit the onset of nerve degeneration due to the disturbances caused by adriamycin and vincristine, and experimental diabetes caused by streptozotocin. Mecobalamin was also compared with steroids in terms of their effects on the process of nerve regeneration in experimental facial paralysis models prepared by compressing the facial nerve of guinea pigs. Mecobalamin was found to be as effective as steroids for the recovery from paralysis when evaluated based on the winking reflex, induced electromyography and histological evaluation.[5).6).]

4. Mecobalamin inhibits abnormal excitation transmission by nerve tissues.
The anterior and posterior roots of the spinal nerve were separated from the spinal cord of frogs and connected to the sciatic nerve. Electrical stimulation was given to the end of the sciatic nerve in Ringer's solution and the action pontentials of the anterior and posterior roots were recorded. 500 µg/ml of DBCC. OH-vitamin $B_{12.}$ CH_3- vitamin B_{12} were dissolved in the Ringer's solution and the inhibition of excitation transmission by these compounds was compared. The inhibition of nervous excitation transmission produced by CH_3 - vitamin B_{12} was strongest.[7)]

Pharmacokinetics

1. **Single dose**
Blood concentration peaked (22310 pg/ml) 0.9 hr after the i.m. injection of a single dose of 500 µg of mecobalamin to healthy adults. The half-life was 6.3 hrs. The Δ C_{max} for the increase in serum total vitamin B_{12} concentration was 21430 pg/ml and the Δ AUC_0^{12} was 185.21 hr. ng/ml.



2. Multiple doses

Patients with peripheral nerve disorders received an i.m. injection of 500 µg of mecobalamin three times per week for 12 weeks. Blood vitamin B_{12} concentration had increased about 15-fold 4 weeks after the start of treatment; it continued to increased thereafter to achieve a 30-fold increase 12 weeks after the start of treatment.[8)]

Clinical Studies

1. Clinical efficacy

Methycobal was found to be useful in patients with peripheral nerve disorders in terms of the overall improvement rate in a double blind clinical trial.[9)]

2. Adverse reactions

Of 1,644 patients treated with Methycobal, only 2 patients (0.12%) of eruption were reported as adverse reactions.

3. Influences on laboratory values

No changes in laboratory values have been associated with Methycobal treatment.

Animal Studies

1. Distribution

In rats given 25 µg/kg of ^{57}Co-labelled mecobalamin intraperitoneally, radioactivity was higher in kidneys, adrenals, liver, and stomach, in order of the magnitude, while muscle, testes, brain and nerve did not show significant radioactivity 72 hours after administration.

2. Acute toxicity Ld_{50} (mg/kg)

Animal	Sex	s.c	i.p.	i.v.	p.o.
Mouse	M.F	> 666	> 666	> 666	> 1.000
Rat	M.F	> 333	> 333	> 333	> 500
Rabbit	M	–	–	> 60	–

3. Subacute toxicity

The continuous intraperitoneal administration to rats of both sexes at dose levels of 0.2, 2.0 and 20 mg/kg/day of mecobalamin for one month, resulted in no remarkable changes in general conditions, body weights, blood, urine, organ weights and histological findings.

4. Chronic toxicity

In rats of both sexes given mecobalamin at doses of 0.2, 2.0 and 20 mg/kg/day for six consecutive months intraperitoneally, no remarkable changes were noted in the general conditions, body weights, blood, urine, organ weights and histological findings.

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5. Reproduction studies

In mature nulliparous mice and rats intraperitoneally administered mecobalamin at dose levels of 0.2, 2.0 and 20 mg/kg/day during organogenesis, no abnormalities or signs of teratogenicity were noted in fetuses or neonates.

Pharmaceutical Description

1. Description of Methycobal injection 500 µg

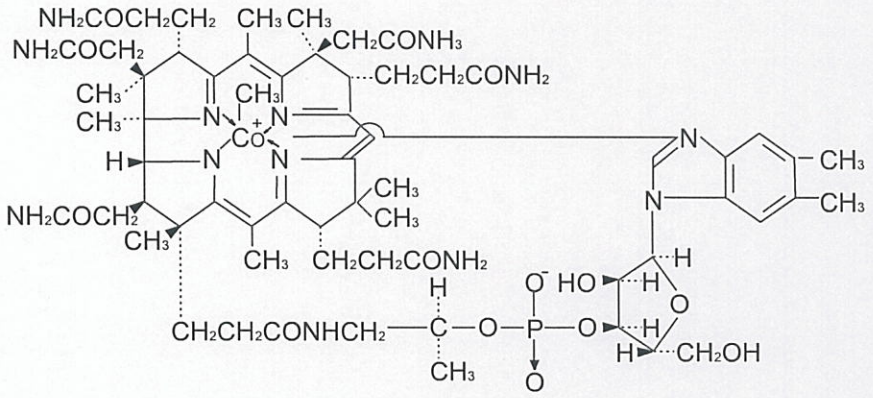
Methycobal injection is a clear, red solution contained in a brown ampule (one-point-cut type).

pH	: 5.3 to 7.3
Osmotic pressure	: About 1 (as compared with that of physiological saline solution)

2. Physico-chemical properties of active ingredient

Generic name	: Mecobalamin
Chemical name	: α-(5, 6-Dimethylbenzimidazolyl)-Co-Methyl-cobamide
Molecular formula	: $C_{63}H_{91}CoN_{13}O_{14}P$
Molecular weights	: 1,344.40

Structural Formula :



Mecobalamin occurs as a dark red, odorless, and almost tasteless crystal or crystalline powder. It is slightly soluble in water, methanol, and ethanol and practically insoluble in aceton, ether and chloroform. It is hygroscopic and decomposes upon exposure to light.

Storage and Handling

1) Methycobal injections are packed with LPE (Light-Protect-Easy Open) to prevent a change in quality during storage, hence, care should be exercised when removing an individual ampule from the package.
2) Protect Methycobal injections from light. Methycobal decomposes due to light, even when in a brown ampule; exposure to light result in a decrease in the content of the active ingredient : store it in the LPE package.
3) Methycobal injection 500 µg should be used before the expiration date stated on the package.
4) Storage : **Preserve at temperature below 30°C in LPE (Light-Protect-Easy Open) packages.**

PACKAGE : In each box : 1 ml X 10 Ampules.

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References
1) Nakazawa, T. et al.: Vitamin 42: 193 (1970)
2) Kuroiwa, Y.: Nervous systems and Methyl B_{12} (Kyowa Kikaku Tsuushin 54 1981)
3) Kuroiwa, Y.: Nervous systems and Methyl B_{12} (Kyowa Kikaku Tsuushin 23 1981)
4) Takenaka, T. et al.: Prog. Med. 2: 1759 (1982)
5) Onishi, A. et al.: Jap. J. Clin. Pharmacol. 10: 247 (1979)
6) Fujita, H. et al.: Pract. Otol. (Kyoto), 77: 1241 (1984)
7) Takeshiga, C. et al.: Vitamin 45: 272 (1971)
8) Tanaka, N. et al.: Vitamin 55: 155 (1981)
9) Kameyama, M. et al.: Jap. J. Clin. Exp. Med. 49: 1967 (1972)

DO NOT DISPENSE WITHOUT PHYSICIANS' PRESCRIPTION
HARUS DENGAN RESEP DOKTER

PERHATIAN : Produk sensitif terhadap cahaya. Gunakan pada ruangan **terhindar dari cahaya.**

Reg. No. XXXXXXXXXXXXXXX

Manufactured by: **Nipro Pharma Corp., Ise Plant,** MIE, JAPAN

Imported & Repacked by
PT Eisai Indonesia
BOGOR, INDONESIA

Eisai

Under License of
Eisai Co., Ltd.
TOKYO, JAPAN

VENDOR CODE

Remark :
1. Dimension : 275 mm X 210 mm ± 20 mm
2. Material : HVS Paper 60 gsm
3. Printing Color : Black