Drug for peripheral neuropathies

Methycobal® injection 500 μg/ml

<Mecobalamin preparation>

Caution: Use only as directed by a physician.

【COMPOSITION】

METHYCOBAL is a clear, red liquid containing the following ingredients, and contained in brown ampoule (one-point-cut type).

Ingredient		Content per ampoule (1 mL)
Active ingredient	Mecobalamin	500 μg
Inactive ingredient	*D*-Mannitol	50 mg
Product description		Methycobal is a clear, red liquid.
pH		5.3-7.3
Osmotic pressure ratio		About 1 (ratio relative to isotonic sodium chloride solution)

【INDICATIONS】

Peripheral neuropathies
Megaloblastic anemia caused by vitamin B_{12} deficiency

<Precautions>
METHYCOBAL should not be used aimlessly for more than one month unless it is effective.

【DOSAGE AND ADMINISTRATION】

- **Peripheral neuropathies**
  The usual dosage for adults is 1 ampoule (500 μg of mecobalamin) per day, administered intramuscularly or intravenously 3 times a week. The dosage may be adjusted depending on the patient's age and symptoms.
- **Megaloblastic anemia**
  The usual dosage for adults is 1 ampoule (500 μg of mecobalamin) per day, administered intramuscularly or intravenously 3 times a week. After about 2 months of medication, the dose should be reduced to a single administration of 1 ampoule at 1 to 3 months intervals for maintenance therapy.

【PRECAUTIONS】

1. **Adverse Reactions**
   Adverse reactions were reported in 13 of 2,872 patients (0.45%). (At the end of the reexamination period)
   (1) Clinically significant adverse reactions (incidence unknown)
   Anaphylactoid reactions
   Anaphylactoid reactions, such as decrease in blood pressure or dyspnea, may occur. Patients should be carefully observed. In the event of such symptoms, treatment should be discontinued immediately and appropriate measures taken.
   (2) Other adverse reactions

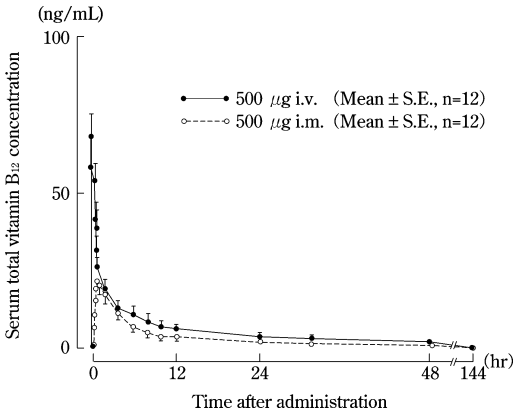
	<0.1%	**Incidence unknown**
Hypersensitivity note)	Rash	
Others	Headache and hot sensation	Diaphoresis and pain / induration at the site of intramuscular injection

Note: In the event of such symptoms, treatment should be discontinued.

2. **Contraindication**
   Hypersensitivity to any form of vitamin B_{12} or D-mannitol.
3. **Interactions with other medicaments**
   Not applicable.
4. **Incompatibility**
   Not applicable.
5. **Statement on usage during pregnancy and lactation**
   Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy. Clinical studies have been done on pregnant women and no harmful effects have been reported. Methycobal with the approved dosage can be used during pregnancy.
   It has been shown that mecobalamin is excreted in the milk of lactating rats.
6. **Overdose and Treatment**
   Experience to date with deliberate or accidental overdose is limited. No specific antidote is known. As in any case of overdose, treatment should be symptomatic and general supportive measures should be utilised.
7. **Precautions concerning Use**
   (1) Administration
   METHYCOBAL is susceptible to photolysis. It should be used promptly after the package is opened, and caution should be taken so as not to expose the ampoules to direct light.
   (2) Intramuscular administration
   In intramuscular administration, caution should be exercised, by following the instructions mentioned below to avoid adverse effects on tissues or nerves.
   1) Avoid repeated injection at the same site. Particular caution should be exercised when administering METHYCOBAL to prematures, neonates, nursing infants and children.
   2) Do not inject in densely innervated site.
   3) If insertion of the injection needle causes intense pain or if blood flows back into the syringe, withdraw the needle immediately and inject at a different site.
   (3) Opening the ampoule
   METHYCOBAL is supplied in one-point-cut ampoules. The cut point of the ampoules should be wiped with an alcohol swab before opening.

【PHARMACOKINETICS】

1. **Single-dose administration**
   Mecobalamin was administered intramuscularly or intravenously to 12 healthy adult male volunteers at a single dose of 500 μg. The time to reach peak serum total vitamin B_{12} (abbreviated to B_{12}) concentration (t_{max}) was 0.9 hr after intramuscular administration and immediately to 3 minutes after intravenous administration, and the increment (except endogenous serum total B_{12}) in peak serum total vitamin B_{12} concentration (ΔC_{max}) was 22.4ng/mL after intramuscular administration and 85.0ng/mL after intravenous administration. The area under the serum total B_{12} concentration-time curve (ΔAUC) calculated by increment of the actual values at 144 hr after administration was 204.1ng·hr/mL after intramuscular administration and 358.6ng·hr/mL after intravenous administration. On the other hand, the rate of binding saturation showed a similar increase in both groups of subjects for 144 hr after administration.



Serum total vitamin B_{12} concentration after single administration of METHYCOBAL Injection 500 μg

Pharmacokinetic parameters after a single dose administration of Methycobal Injection 500 μg

	t_{max} (hr)	ΔC_{max} (ng/mL)	ΔAUC_0^{144} (ng·hr/mL)	$t_{1/2}$ (hr)
I.V.	0 - 3 min	85.0±8.9	358.6±34.4	27.1
I.M.	0.9±0.1	22.4±1.1	204.1±12.9	29.0

Mean ± S.E., n=12

2. **Repeated-dose administration**
   Mecobalamin was administered intravenously to 6 healthy adult male volunteers at a single dose of 500 μg daily for 10 consecutive days. Serum total vitamin B_{12} concentration determined before each administration increased from day to day. After 2 days of administration, the serum total vitamin B_{12} concentration was 5.3±1.8ng/mL, about 1.4 times the 24 hr value (3.9±1.2ng/mL) after administration. At 3 days of administration it had increased to 6.8±1.5ng/mL, about 1.7 times the 24 hr value, and this concentration was maintained until the last dosing.

【CLINICAL STUDIES】

Clinical efficacy
Mecobalamin was administered intramuscularly to patients with peripheral neuropathies in single doses of 500 μg and 100 μg (low-dose group) daily 3 times a week for 4 consecutive weeks in a double-blind clinical trial. In the chronic stage and fixed stage of peripheral neuropathies in the 500 μg group aggravation of symptoms was significantly suppressed compared to the low-dose group and this dose was thus demonstrated to be useful.
In a placebo-controlled double-blind clinical trial, mecobalamin was administered intravenously or intramuscularly to patients with peripheral neuropathies at a single dose of 500 μg daily 3 times a week for 4 consecutive weeks. The improvement rate for intravenous administration was 38.7% (24/62) for moderately to remarkably improved and 74.2% (46/62) for fairly to remarkably improved. The improvement rate for intramuscular administration was 46.3% (25/54) for moderately to remarkably improved and 81.5% (44/54) for fairly to remarkably improved. The equivalence of mecobalamin efficacy for both administration routes was thus demonstrated. The diseases of subjects in the trial were diabetic neuropathy, polyneuritis, cervical spondylosis, sciatica, alcoholic neuropathy, facial paralysis and mononeuritis, etc.
When mecobalamin was administered to patients with megaloblastic anemia due to vitamin B_{12} deficiency, their hemograms and symptoms improved in 3 weeks to 2 months after starting administration.

【PHARMACOLOGY】

1. **Mecobalamin is a kind of endogenous coenzyme B_{12}**
   Mecobalamin plays an important role in transmethylation as a coenzyme of methionine synthetase in the synthesis of methionine from homocysteine.
2. **Mecobalamin is well transported to nerve cell organelles, and promotes nucleic acid and protein synthesis.**
   Mecobalamin is better transported to nerve cell organelles than cyanocobalamin in rats. It has been shown in experiments with cells from the brain origin and spinal nerve cells in rats to be involved in the synthesis of thymidine from deoxyuridine, promotion of deposited folic acid utilization and metabolism of nucleic acid. Also, mecobalamin promotes nucleic acid and protein synthesis in rats more than cobamamide does.
3. **Mecobalamin promotes axonal transport and axonal regeneration.**
   Mecobalamin normalizes axonal skeletal protein transport in sciatic nerve cells from rat models with streptozotocin-induced diabetes mellitus. It exhibits neuropathologically and electrophysiologically inhibitory effects on nerve degeneration in neuropathies induced by drugs, such as adriamycin, acrylamide, and vincristine (in rats and rabbits), models of axonal degeneration in mice and neuropathies in rats with spontaneous diabetes mellitus.
4. **Mecobalamin promotes myelination (phospholipid synthesis).**
   Mecobalamin promotes the synthesis of lecithin, the main constituent of medullary sheath lipid and increases myelination of neurons in rat tissue culture more than cobamamide does.
5. **Mecobalamin restores delayed synaptic transmission and diminished neurotransmitters to normal.**
   Mecobalamin restores end-plate potential induction early by increasing nerve fiber excitability in the crushed sciatic nerve in rats. In addition, mecobalamin normalizes diminished brain tissue levels of acetylcholine in rats fed a choline-deficient diet.
6. **Mecobalamin promotes the maturation and division of erythroblasts, thereby alleviating anemia.**
   It is well known that vitamin B_{12}-deficiency may cause specific megaloblastic anemia. Mecobalamin promotes nucleic acid synthesis in bone marrow and promotes the maturation and division of erythroblasts, thereby increasing erythrocyte production. Mecobalamin brings about a rapid recovery of diminished red blood cell, hemoglobin, and hematocrit in vitamin B_{12}-deficient rats.

【STORAGE AND HANDLING】

- **Cautions**
  METHYCOBAL is packaged in LPE packs (Light Protect Easy open pack) to ensure quality during storage. The LPE pack should be opened immediately before using.
- **Storage**
  METHYCOBAL should be stored below 30°C and protected from light.
- **Expiration date**
  METHYCOBAL should be used before the expiration date specified on the package or label.

【PACKAGING】

METHYCOBAL Injection 500 μg (1 mL)
Boxes of 10 ampoules

【NOTE】

Manufactured by:
Nipro Pharma Corporation Ise Plant
647-240, Ureshinotengeji-cho, Matsusaka-shi, Mie, Japan
under license of Eisai Co., Ltd.

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