A Drug for Peripheral Neuropathies

Methycobal® 500μg

TABLETS

(Mecobalamin Preparation)

Composition

Each tablet contains 500 μg of mecobalamin.

It also contains carnauba wax, microcrystalline cellulose, titanium oxide, stearic acid, calcium stearate, sucrose, talc, precipitated calcium carbonate, corn starch, lactose hydrate, white shellac, hydroxypropylcellulose, pullulan, povidone, macrogol 6000 and hydrated silicon dioxide as inactive ingredients.

Indications

Peripheral neuropathies

Dosage and Administration

The usual daily dose for adults is 3 tablets, equivalent to a total of 1,500 μg of mecobalamin, administered orally in 3 divided doses. The dose may be adjusted according to the age of patient and severity of symptoms.

Precautions

1. **General**
   Methycobal should not be administered for extensive periods (months) to patients who show no clinical response.
2. **Precautions concerning Use**
   Caution in handing over drug
   For drugs that are dispensed in a press-through package (PTP), instruct the patient to remove the drug from the package prior to use. [It has been reported that, if the PTP sheet is swallowed, the sharp corners of the sheet may puncture the esophageal mucosa, causing perforation and resulting in serious complications such as mediastinitis.]
3. **Other Precautions**
   Prolonged use of larger doses of Methycobal is not recommended for patients whose occupation requires handling mercury or its compounds.

Adverse reactions

Adverse reactions were reported in 146 of 15,180 patients (0.96%). (At the end of the investigation for incidence of adverse reactions)

	5% > ≥0.1%	<0.1%
Gastrointestinal	Anorexia, nausea/vomiting and diarrhea	
Hypersensitivity note)		Rash

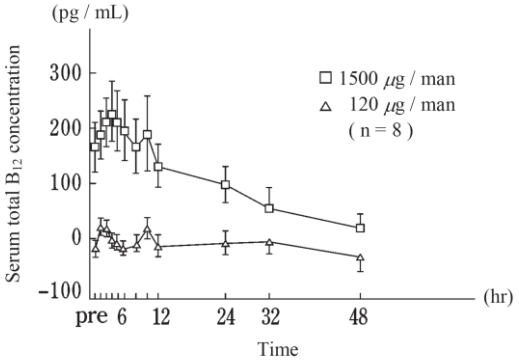
Note) In the event of such symptoms, Methycobal should be discontinued.

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 lipids, 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.

Pharmacokinetics

1. **Single dose administration**
   When Methycobal was administered orally to healthy adult male volunteers at single doses of 120 μg and 1,500 μg note) during fasting, the peak serum total vitamin B_{12} (abbreviated to B_{12}) concentration was reached after 3 hrs for both doses, and this was dose-dependent. The half-life, increment in the serum total B_{12} concentration and ΔAUC_0^{12} by 12 hrs after administration are shown in the following figure and table. 40 to 90% of the cumulative amount of total B_{12} excreted in the urine by 24 hrs after administration was excreted within the first 8 hrs.
   Note) A single dose of 1,500 μg is unapproved.



Increment in total serum B_{12} concentration

Dose	t_{max} (hr)	C_{max} (pg/mL)	ΔC_{max} (pg/mL)	ΔC_{max} (%)	ΔAUC_0^{12*1} (pg·hr /mL)	$t_{1/2}^{*2}$ (hr)
120 μg	2.8±0.2	743±47	37±15	5.1±2.1	168±58	N.A.
1500 μg	3.6±0.5	972±55	255±51	36.0±7.9	2033±510	12.5

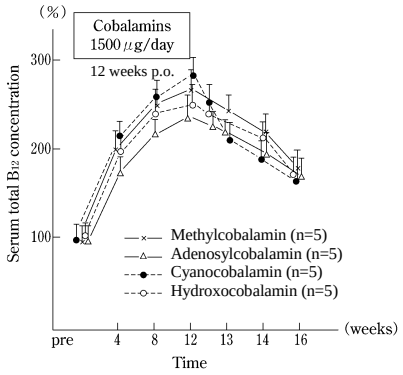
Mean±S.E., n=8

*1 Calculated by the trapezoidal formula from the increment in observed 12 hr values, as compared to pre-drug values.

*2 Calculated from the average of 24-48 hr values.

2. Repeated dose administration

Methycobal was administered orally to healthy adult male volunteers at a dose of 1,500 μg daily for 12 consecutive weeks and changes in the serum total B_{12} concentration were determined until 4 weeks after the last administration. The serum concentration increased for the first 4 weeks after administration, rising to about twice as high as the initial value. Thereafter, there was a gradual increase which peaked at about 2.8 times the initial value at the 12th week of dosing. The serum concentration declined after the last administration (12 weeks), but was still about 1.8 times the initial value 4 weeks after the last administration.



Clinical Studies

Mecobalamin was administered orally to patients with peripheral neuropathies at doses of 1,500 μg and 120 μg (low-dose group) daily divided into three doses for 4 consecutive weeks in a double-blind clinical trial. In the chronic stage and fixed stage in peripheral neuropathies, the improvement rate for moderately to remarkably improved was 17.6% (6/34) in 1,500 μg group and 9.7% (3/31) in 120 μg group. The improvement rate for fairly to remarkably improved was 64.7% (22/34) in the 1,500 μg group and 41.9% (13/31) in the 120 μg group. The dose of 1,500 μg/day was thus demonstrated to be useful. In a placebo-controlled double-blind clinical trial, mecobalamin and cobamamide were administered orally to patients with peripheral neuropathies at doses of 1,500 μg daily for 4 consecutive weeks. The rates for moderately to remarkably improved for peripheral neuropathies were 38.6% (17/44) for mecobalamin, 22.2% (10/45) for cobamamide and 26.7% (12/45) for placebo. Mecobalamin was thus demonstrated to be useful.

Pharmaceutical Description

Description of Methycobal

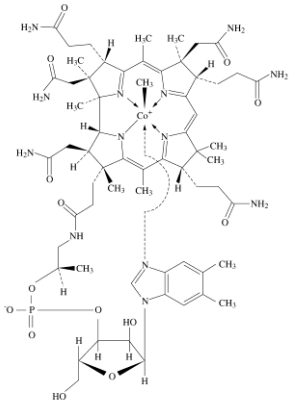
Methycobal Tablets 500 μg are white, sugar-coated tablets.

Identification code	Face	Reverse side	Lateral side
∈ 322	∈ 322		
Diameter: 7.3 mm, Weight: 155 mg, Thickness: 4.0 mm			

Physicochemistry

Nonproprietary name: Mecobalamin (JAN, INN)
Chemical name: *Co*α-[α-(5, 6-Dimethyl-1*H*-benzoimidazol-1-yl)]-*Co*β-methylcobamide
Molecular formula: $C_{63}H_{91}CoN_{13}O_{14}P$
Molecular weight: 1344.38

Structural formula:



Description:

Mecobalamin occurs as dark red crystals or crystalline powder. It is sparingly soluble in water, slightly soluble in ethanol (99.5), and practically insoluble in acetonitrile. It is degraded by light.

Storage

1. Methycobal Tablets should be stored below 30℃.
2. Methycobal Tablets should be protected from moisture and light. (Light decomposes the active ingredient and the tablets may turn reddish with humidity).

Expiration date

Methycobal Tablets should be used before the expiration date stated on the package.

Packaging:

100 Tablets (10x 10's)

Manufactured by:

Bushu Pharmaceuticals Ltd. Misato Factory
950, Hiroki, Ohaza, Misato-machi, Kodama-gun, Saitama-ken, Japan

Product owner:

Eisai Co., Ltd.
4-6-10 Koishikawa, Bunkyo-ku,
Tokyo, Japan

Date of PI revision:

November 2015