

Revised: June 2007 (9th version)

Standard Commodity Classification No. of Japan
873136

- Drug for peripheral neuropathies -

Methycobal[®] Tablets 250 µg**Methycobal**[®] Tablets 500 µg**Methycobal**[®] Fine Granules 0.1 %

<Mecobalamin preparation>

Storage
1. METHYCOBAL should be stored at room temperature. 2. Sugar-coated tablets should be protected from light and moisture after opening package. (Light decreases the content and tablets may turn reddish with exposure to moisture.) 3. Fine granules should be protected from light after opening package.

	Tablets 250 µg	Tablets 500 µg	Fine granules 0.1%
Approval No.	54AM-1326	54AM-1327	21900AMX00012000
Date of listing in the NHI reimbursement price	Jun 1984	Sep 1981	Jun 2007
Date of initial marketing in Japan	Jun 1984	Sep 1981	Jul 1984

Expiration date
METHYCOBAL should be used before the expiration date indicated on the package.

DESCRIPTION**1. Composition****Tablets 250 µg:**

Each white sugar-coated tablet contains 250 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.

Tablets 500 µg:

Each white sugar-coated 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.

Fine granules 0.1 %:

Each gram of pink-red fine granules contains 1,000 µg (1 mg) of mecobalamin.

It also contains hydrated silicon dioxide, microcrystalline cellulose, Food Red No.102 (New coccine), corn starch, hydroxypropylcellulose and D-mannitol as inactive ingredients.

2. Product description

Brand name	Dosage form and identification code	Appearance			Description
		Face	Reverse	Lateral	
METHYCOBAL Tablets 250 µg	Sugar-coated tablets				White
	E 321	Diameter (mm) 6.2	Weight (mg) 95	Thickness (mm) 3.4	
METHYCOBAL Tablets 500 µg	Sugar-coated tablets				White
	E 322	Diameter (mm) 7.3	Weight (mg) 155	Thickness (mm) 4.0	
METHYCOBAL Fine granules 0.1%	Fine granules				Pink-red

INDICATIONS

Peripheral neuropathies

<Precautions>

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

DOSAGE AND ADMINISTRATION**Tablets 250 µg:**

The usual adult dosage for oral use is 6 tablets (1,500 µg of mecobalamin) daily divided into three doses.

The dosage may be adjusted depending on the patient's age and symptoms.

Tablets 500 µg:

The usual adult dosage for oral use is 3 tablets (1,500 µg of mecobalamin) daily divided into three doses.

The dosage may be adjusted depending on the patient's age and symptoms.

Fine granules 0.1 %:

The usual adult dosage for oral use is 3 packets (1,500 µg of mecobalamin) daily divided into three doses.

The dosage may be adjusted depending on the patient's age and symptoms.

PRECAUTIONS

1. 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)¹⁾

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

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

2. Precautions concerning Use

Caution in handing over drug (tablets)

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

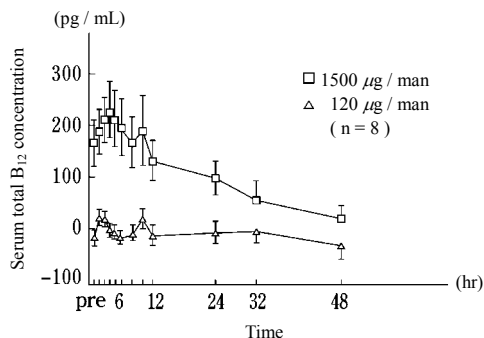
The prolonged use of larger doses of METHYCOBAL is not recommended for patients whose occupation requires the handling of mercury or mercury compounds.

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 B₁₂ (abbreviated to B₁₂) concentration was reached after 3 hrs for both doses, and this was dose-dependent. The half-life, increment in the serum total B₁₂ concentration and ΔAUC₀¹² by 12 hrs after administration are shown in the following figure and table. Forty to eighty percent of the cumulative amount of total B₁₂ excreted in the urine by 24 hrs after administration was excreted within the first 8 hrs.²⁾

Note) A single dose of 1,500 µg is unapproved.



Increment in total serum B₁₂ 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

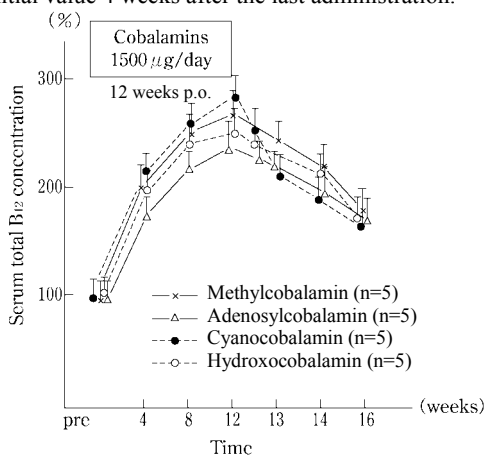
Mean±S.E., n=8

*1 Calculated by the trapezoidal method 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 B₁₂ 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.³⁾



CLINICAL STUDIES

Clinical efficacy

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.⁴⁾ 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.⁵⁾

PHARMACOLOGY

1. Mecobalamin is a kind of endogenous coenzyme B₁₂

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.⁶⁻⁸⁾

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.⁹⁻¹⁴⁾

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 cobamide does.^{15, 16)}

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.^{17, 18)}

PHYSICOCHEMISTRY

Nonproprietary name: Mecobalamin (JAN, INN)

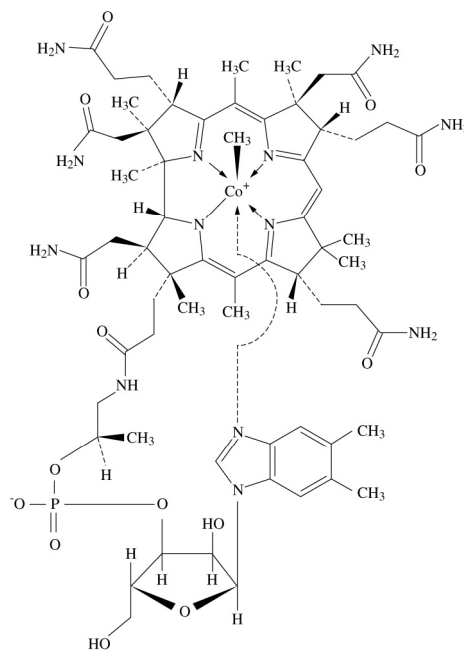
Chemical name:

*Co*α-[α-(5,6-Dimethylbenz-1*H*-imidazolyl)]-*Co*β-methylcobamide

Molecular formula: C₆₃H₉₁CoN₁₃O₁₄P

Molecular weight: 1,344.38

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 affected by light.

PACKAGING

Tablets 250 µg:

Boxes of 100 and 1,000 in press through packages, and bottles of 500

Tablets 500 µg:

Boxes of 100, 210 (21 Tabs. × 10), 1,000, 1,050 (21 Tabs. × 50) and 3000 in press-through packages, and bottles of 500 and 3,000

Fine granules 0.1 %:

Boxes of 60 g (0.5 g packet × 3 × 40)

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Fax: 03-3811-2710

Eisai Co., Ltd.

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Customer Information Services Section

Free Dial: 0120-419-497

Eisai Co., Ltd.

Manufactured and marketed by:

Eisai Co., Ltd.

6-10, Koishikawa 4-chome, Bunkyo-ku, Tokyo, 112-8088