PACKAGE INSERT TEMPLATE FOR MECOBALAMIN INJECTION

Brand or Product Name
[Product name] Injection 500μg

Name and Strength of Active Substance(s)
Mecobalamin ….mg

Product Description
[Visual description of the appearance of the product (eg colour etc)]
eg Clear, red injection contained in brown ampoule (one-point-cut type).

Pharmacodynamics

(1) *Mecobalamin is a kind of endogenous coenzyme B12 :*
As a coenzyme of methionine synthetase, mecobalamin plays an important role in transmethylation in the synthesis of methionine from homocysteine.

(2) *Mecobalamin is well transported to nerve cell organelles, and promotes nucleic acid and protein synthesis :*
Experiments in rats show that mecobalamin is better transported to nerve cell organelles than cyanocobalamin and promotes nucleic acid and protein synthesis more than cobamamide does.
Experiments with cells from the brain origin and spinal nerve cells in rats also show mecobalamin to be involved in the synthesis of thymidine from deoxyuridine, promotion of deposited folic acid utilization and metabolism of nucleic acid.

(3) *Mecobalamin promotes axonal transport and axonal regeneration :*
In rat models with streptozotocin-induced diabetes mellitus, mecobalamin normalizes axonal skeletal protein transport in sciatic nerve cells. Mecobalamin 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 which is the main constituent of medullary sheath lipid. It also increases myelination of neurons in rat tissue culture more than cobamamide does.

(5) *Mecobalamin restores delayed synaptic transmission and diminished neurotransmitters back 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 levels of acetylcholine in brain tissue of rats fed with a choline-deficient diet.

(6) *Mecobalamin promotes the maturation and division of erythroblasts, thereby alleviating anaemia :*
Vitamin B12-deficiency may cause specific megaloblastic anaemia. Mecobalamin promotes nucleic acid synthesis in bone marrow and the maturation and division of erythroblasts, thereby increasing erythrocyte production. In vitamin B12-deficient rats, administration of mecobalamin results in a rapid recovery of diminished red blood cell, haemoglobin, and haematocrit.

Pharmacokinetics

(1) Absorption
Vitamin B12 substances bind to intrinsic factor, a glycoprotein secreted by the gastric mucosa, and are then actively absorbed from the gastrointestinal tract. Absorption is impaired in patients with an absence of intrinsic factor, with a malabsorption syndrome or with disease or abnormality of the gut, or after gastrectomy. Absorption from the gastrointestinal tract can also occur by passive diffusion; little of the vitamin present in food is absorbed in this manner although the process becomes increasingly important with larger amounts such as those used therapeutically.

(i) Single-dose administration
When 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 B12 concentration (tmax) was 0.9 hr after intramuscular administration and immediately to 3 min after intravenous administration, and the increment (except endogenous serum total B12) in peak serum total vitamin B12 concentration (ΔCmax) was 22.4 ng/mL after intramuscular administration and 85.0 ng/mL after intravenous administration. The area under the serum total B12 concentration-time curve (ΔAUC) calculated by increment of the actual values at 144 hr after administration was 204.1 ng · hr/mL after intramuscular administration and 358.6 ng · 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.

(ii) Repeated-dose administration
When mecobalamin was administered intravenously to 6 healthy adult male volunteers at a single dose of 500 μg daily for 10 consecutive days. Serum total B12 concentration determined before each administration increased from day to day. After 2 days of administration, the serum total B12 concentration was 5.3±1.8 ng/mL, about 1.4 times the 24 hr value (3.9±1.2 ng/mL) after administration. At 3 days of administration it had increased to 6.8±1.5 ng/mL, about 1.7 times the 24 hr value, and this concentration was maintained until the last dosing.

(2) Distribution
Vitamin B12 is extensively bound to specific plasma proteins called transcobalamins; transcobalamin II appears to be involved in the rapid transport of the cobalamins to tissues. Vitamin B12 is stored in the liver. Vitamin B12 diffuses across the placenta and also appears in breast milk.

(3) Excretion
Vitamin B12 is excreted in the bile, and undergoes extensive enterohepatic recycling; part of a dose is excreted in the urine, most of it in the first 8 hours; urinary excretion, however, accounts for only a small fraction in the reduction of total body stores acquired by dietary means.

(4) Elimination Half-life
27.1 hrs (single-dose I.V. administration)
29.0 hrs (single-dose I.M. administration)

Indication
Peripheral neuropathies
Megaloblastic anaemia caused by vitamin B12 deficiency

Recommended Dosage

Adult Dosage
Injection 500μg
• *Peripheral neurophathies*
The usual dosage for adults is 1 ampoule (500 μg of mecobalamin) daily, 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) daily, administered intramuscularly or intravenously 3 times a week. After about 2 months of medication, the dose should be reduced to a single administration of 1ampoule at 1 to 3 months intervals for maintenance therapy.

Mode of administration
Intramuscular, intravenous

Contraindications
Hypersensitivity to mecobalamin or other components of the formulation.

Warnings and Precautions

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

Vitamin B12 should, if possible, not be given to patients with suspected vitamin B12 deficiency without first confirming the diagnosis. Where it is desirable to start therapy immediately, combined treatment for both deficiencies may be started once suitable samples have been taken to permit diagnosis of the deficiency, and the patient converted to the appropriate treatment once the cause of the anaemia is known. Regular monitoring of the blood is advisable.

Although the haematological symptoms of B12 deficiency and folate deficiency are similar, it is important to distinguish between them since the use of folate alone in B12-deficient

megaloblastic anaemia can improve haematological symptoms without preventing aggravation of accompanying neurological symptoms, and may lead to severe nervous system sequelae such as subacute combined degeneration of the spinal cord. Use of doses greater than 10 micrograms daily may produce a haematological response in patients with folate deficiency and indiscriminate use may mask the precise diagnosis. Conversely, folate may mask vitamin B12 deficiency.

Precautions concerning use
(1) Administration
Mecobalamin is susceptible to photolysis and the ampoules are packaged in the light-proof packaging to ensure the quality during storage. If ampoules are not kept in the light-proof packaging, mecobalamin decomposes by light and the content decreases. Therefore, this product 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, the following precautions should be taken to avoid adverse effects on tissues or nerves :
(i) Avoid repeated injection at the same site. Particular caution should be exercised when administering the product to prematures, neonates, nursing infants and children.
(ii) Do not inject in densely innervated site.
(iii) 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
The cut point of the ampoules should be wiped with an alcohol swab before opening.

Interactions with Other Medicaments

Serum concentrations may be decreased by use of oral contraceptives.

Parenteral chloramphenicol may attenuate the effect of vitamin B12 in anaemia.

Many of these interactions are unlikely to be of clinical significance but should be taken into account when performing assays for blood concentrations.

Statement on Usage During Pregnancy and Lactation

Pregnancy
There are no data available for mecobalamin to be used in pregnant women.

Lactation
There are no data available for mecobalamin to be used in lactating women. However, since vitamin B12 is distributed into breast milk, The American Academy of Pediatrics considers its use to be usually compatible with breast feeding.

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Adverse Effects / Undesirable Effects

Dermatologic Effects: Rash ; In the event of such symptoms, treatment should be discontinued.

Gastrointestinal Effects: Anorexia, nausea/vomiting and diarrhea

Neurologic Effects (Central nervous system): Headache

Others:

- Anaphylactoid reaction : 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.

- Hot sensation

- Diaphoresis

- Pain/induration at the site of intramuscular injection

Overdose and Treatment
There have been no reports, in the literature, of overdosage with mecobalamin.

Storage Conditions
[eg. Store below….□ C ; Ampoules (injection) should be stored in the light-proof packaging.]

Dosage Forms and Packaging Available
[Packaging type & pack size]

Name and Address of Manufacturer
[Name & full address of manufacturer]

Name and Address of Marketing Authorization Holder
[Name & full address of marketing authorization holder]

Date of Revision of Package Insert
[day/month/year]