Mobicol INJECTION / TABLET

(M e c o b a l a m i n)

موبیکول انجیکشن / ٹیبلیٹ

(میکوبالامین)

COMPOSITION

MOBICOL Injection 500mcg/ml:

Each 1ml ampoule contains:

Mecobalamin 500mcg

(Innovator's Specifications)

MOBICOL Tablet500mcg:

Each sugar coated tablet contains:

Mecobalamin 500mcg

(JP Specifications)

DESCRIPTION

MOBICOL is a clear, red liquid containing mecobalamin **Methylcobalamin** (mecobalamin, MeCbl, or MeB_{12}) is a cobalamin, a form of vitamin B_{12}, occurring in the blood and cerebrospinal fluid, Mecobalamin is transported to nerve tissues better than other types of vitamin B12. It differs from cyanocobalamin in that the cyanide is replaced by a methyl group. Methylcobalamin can be obtained as bright red crystals. Biochemically, MOBICOL promotes nucleic acid, protein and lipid metabolism through transmethylation reactions. Pharmacologically, mecobalamin repairs injured nerve tissues and inhibits abnormal impulse conduction of methanogenesis.

Mecobalamin promotes the maturation and division of erythroblast and heme synthesis, thereby improving the hemogram in anemia. Clinically, MOBICOL has been shown to benefit megaloblastic anemia and peripheral neuropathies such as diabetic neuropathy and polyneuritis. MOBICOL is the vitamin B12 preparation clinically proven to be effective by double-blind clinical trials.

INDICATIONS

- Peripheral neuropathies
- Diabetic neuropathy
- Megaloblastic anemia caused by vitamin B12 deficiency
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CLINICAL PHARMACOLOGY

Mechanism of Action

Vitamin B12 is used in the body in two forms, methylcobalamin and 5-deoxyadenosyl cobalamin. The enzyme methionine synthase needs methylcobalamin as a cofactor. This enzyme is involved in the conversion of the amino acid homocysteine into methionine which is, in turn, required for DNA methylation. The other form, 5-deoxyadenosylcobalamin, is a cofactor needed by the enzyme that converts L-methylmalonyl-CoA to succinyl-CoA. This conversion is an important step in the extraction of energy from proteins and fats. Furthermore, succinyl CoA is necessary for the production of hemoglobin, the substance that carries oxygen in red blood cells.

Vitamin B12, or methylcobalamin, is essential to growth, cell reproduction, hematopoiesis, and nucleoprotein and myelin synthesis. Cells characterized by rapid division (epithelial cells, bone marrow, myeloid cells) appear to have the greatest requirement for methylcobalamin. Vitamin B12 can be converted to coenzyme B12 in tissues; in this form it is essential for conversion of methylmalonate to succinate and synthesis of methionine from homocysteine (a reaction which also requires folate). In the absence of coenzyme B12, tetrahydrofolate cannot be regenerated from its inactive storage form, 5-methyl tetrahydrofolate, resulting in functional folate deficiency. Vitamin B12 also may be involved in maintaining sulfhydryl (SH) groups in the reduced form required by many SH-activated enzyme systems. Through these reactions, vitamin B12 is associated with fat and carbohydrate metabolism and protein synthesis. Vitamin B12 deficiency results in megaloblastic anemia, GI lesions, and neurologic damage (which begins with an inability to produce myelin and is followed by gradual degeneration of the axon and nerve head). Vitamin B12 requires an intrinsic factor-mediated active transport for absorption, therefore, lack of or inhibition of intrinsic factor results in pernicious anemia.

HOW IT WORKS

- Assists in the reduction of elevated Homocysteine. Elevated Homocysteine has been linked to increased cardiovascular risk of disease.
- Proven beneficial for symptoms of depression (i.e., supporting the production of serotonin and melatonin) acts as a methyl donor and participates in the synthesis of SAM-e (S-adenosylmethionine), a nutrient that has powerful mood elevating properties.
- Supports Immune system regulation
- Repair of damaged myelin sheath acts to reverse nerve damage and promote nerve cell regeneration
- Increased metabolic function
- Supports healthy red blood cells and is used to treat Anemia
- Protects against neurological disease and aging
- Improvement of mental dysfunction in the elderly
- Supportive treatment in HIV
- Useful in protocols for asthma and sulfite sensitivities necessary for the conversion of methylmalonate to succinic acid, an important Krebs cycle intermediate in energy production.

DOSAGE AND ADMINISTRATION

- ***For injection***

Peripheral neuropathies

The usual dose for adults is 1 ampoule (500 µg of mecobalamin) a day, administered intramuscularly or intravenously three times a week.

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

Megaloblastic anemia

The usual dose for adults is 1 ampoule (500 µg of mecobalamin) a day, administered intramuscularly or intravenously three times a week. After approximately **2 months of medication,** the dose should be reduced to a single administration of ampoule at **1 to 3 months** intervals for maintenance therapy.

- ***For Tablet***

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.

- **PRECAUTIONS**

➢ **Adverse Reaction** (rarely :< 0. 1 %, infrequently 0. 1% - < 5 %, no specific designation : ^ 5% or frequency unknown)

- **Hypersensitivity**

Use of this product should be discontinued if symptoms of hypersensitivity, such as rash, occur.

- **Others**

Pain and induration may occur infrequently at the site of intramuscular injection. Headache, diaphoresis or hot sensation may occur rarely.

➢ **Cautions in Use**

- **Caution in administration**

MOBICOL is susceptible to photolysis. It must be used promptly after the package is opened, and care must be taken not to expose the ampoules to direct light.

- **Cautions in intramuscular administration.**

In intramuscular administration, care should be exercised, by following the instructions mentioned below, to avoid adverse effects on tissues or nerves.

✓ Avoid repeated injection at the same site. Particular care should be exercised when administering this product to neonates, premature infants, infants and children.

✓ Do not inject at innervated site.

✓ If insertion of the injection needle evokes intense pain, or if blood flow back into the syringe, withdraw the needle immediately and inject at a different site.

- **Caution in use the one-point-cut ampoule**

The product is supplied as one-point-cut ampoules. The cut point of the ampoules should be wiped with an alcohol swab before opening.

ADVERSE REACTIONS

Oral: Anorexia, nausea, vomiting and diarrhoea.

Parenteral: Rash, headache, hot sensation, diaphoresis and pain/induration at IM inj site. Potentially Fatal: Anaphylactoid reactions (parenteral).

PHARMACOKINETICS

➢ **Single-dose administration**

When a single i.m. or i.v. of 500 ug of CH3-B12 was administered to healthy adult volunteers, the time required for the serum total vitamin B12 level to reach a peak (T max) was 0.9_+ 0.1_hour after i.m. administration and immediately to 3 min. after i.v. administration, and the increment in peak serum total vitamin B12 level (AC max) was 22.4_+ 1.1 ng/ml after i.m. administration and 85.0 + 8.9 ng/ml after i.v. administration. The area under the blood concentration-time curve (^AUC) at 144 hours after administration was 204 .1 + 12.9 hr. ng/ml after i.m. administration and 358.6 + 34.4 hr. ng/ml after i.v. administration.

On the other hand, the rate of binding saturation showed a similar increase in both groups of subjects for 144 hours after administration. Excretion occurs by urine Time after Administration (hr.)

➢ **Repeated-dose administration**

500 ug/day of CH3 - B12 was administered intravenously to healthy adult volunteers for 10 consecutive days. Serum total vitamin B12 levels measured before each administration (A C min) increased from day to day. After 2 days of administration, the serum level of total vitamin B12 was 5.3 ± 1.8 ng/ml, about 1.4 times the 24-hour value (3.9 ± 1.2 ng/ml). At 3 days of administration it was increased to 6.8 ±1.5 ng/ml, about 1.7 times the 24-hour value, and this level was maintained until the last dosing. Excretion occurs by urine

➢ **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.

➢ **Single-dose administration**

When mecobalamin was administered orally to healthy adult male volunteers

at single doses of 120 µg and 1,500 µg) during fasting, the peak serum total vitamin B12 concentration was reached after 3 hrs for both doses, and this was dose-dependent. Note) A single dose of 1,500 µg is unapproved.

➢ **Repeated-dose administration**

When mecobalamin was administered orally to healthy adult male volunteers at a dose of 1,500 µg daily for 12 consecutive weeks, 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.

➢ **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.

➢ **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. 40-80% of the cumulative amount of total B12 excreted in the urine by 24 hrs after single-dose administration was excreted within the first 8 hrs. Elimination Half-life 12.5 hrs (single-dose oral administration; calculated from the average of 24-48 hour values)

CONTRAINDICATION

MOBICOL is contraindicated in conditions like:

- Methylcobalamin is contraindicated in patients with methylcobalamin hypersensitivity or hypersensitivity to any of the medication components.
- Methylcobalamin is also contraindicated in patients with cobalt hypersensitivity because methylcobalamin contains cobalt. In the case of suspected cobalt hypersensitivity, an intradermal test dose should be administered because anaphylactic shock and death have followed parenteral administration of methylcobalamin
- Methylcobalamin should not be used in patients with early hereditary optic nerve atrophy (Leber's disease). Optic nerve atrophy can worsen in patients whose methylcobalamin levels are already elevated. Hydroxocobalamin is the preferred agent in this patient population (see separate monograph in Less Common Drugs).
- Most formulations of methylcobalamin injection contain benzyl alcohol as a preservative. Benzyl alcohol may cause allergic reactions.
- Methylcobalamin injections should be used cautiously in those patients with benzyl alcohol hypersensitivity. Methylcobalamin, vitamin B12 preparations containing benzyl alcohol should be avoided in premature neonates because benzyl alcohol has been associated with 'gasping syndrome,' a potentially fatal condition characterized by metabolic acidosis and CNS, respiratory, circulatory, and renal dysfunction.
- Vitamin B12 deficiency can suppress the symptoms of polycythaemia vera.
- Treatment with methylcobalamin or hydroxocobalamin may unmask this condition.
- Folic Acid, vitamin B9 is not a substitute for methylcobalamin, vitamin B12 deficiency, although it may improve vitamin B12 megaloblastic anemia.
- However, exclusive use of folic acid in treating vitamin B12 deficient megaloblastic anemia could result in progressive and irreversible neurologic damage. Before receiving folic acid or methylcobalamin, patients should be assessed for deficiency and appropriate therapy started concurrently. The intranasal formulations are not approved to treat acute B12 deficiency; all hematologic parameters should be normal before beginning the methylcobalamin intranasal formulations. Concurrent iron-deficiency anemia and folic acid deficiency may result in a blunted or impeded response to methylcobalamin therapy.
- Certain conditions may blunt or impede therapeutic response to methylcobalamin therapy. These include serious infection, uraemia or renal failure, drugs with bone marrow suppression properties (e.g., chloramphenicol), or concurrent undiagnosed folic acid or iron deficiency anemia. The mechanism appears to be interference with erythropoiesis. Patients with vitamin B12 deficiency and concurrent renal or hepatic disease may require increased doses or more frequent administration of methylcobalamin.

DRUG INTERACTIONS

- Several drugs, including para-amino salicylic acid, have been reported to reduce the absorption of methylcobalamin, vitamin B12. Monitor for the desired therapeutic response to vitamin B12.
- The heavy consumption of ethanol for greater than 2 weeks has been reported to reduce the absorption of Methylcobalamin, vitamin B12. Patients should be aware that heavy, chronic ethanol use may counteract the therapeutic effects of vitamin B12; such patients with regular and chronic ethanol consumption be monitored for the desired therapeutic response to vitamin B12.
- Several drugs, including colchicine, have been reported to reduce the absorption of methylcobalamin, vitamin B12. Colchicine has been shown to induce reversible malabsorption of vitamin B12, apparently by altering the function of ileal mucosa. Although further study of these interactions is necessary, patients receiving these agents concurrently should be monitored for the desired therapeutic response to vitamin B12.
- In a study of 10 healthy male volunteers, omeprazole, in doses of 20 mg—40 mg per day, caused a significant decrease in the oral absorption of methylcobalamin, vitamin B12. Theoretically this interaction is possible with other proton pump inhibitors (PPIs), although specific clinical data are lacking. Patients receiving long-term therapy with omeprazole or other proton pump inhibitors (PPIs) should be monitored for signs of B12deficiency.
- Chloramphenicol can antagonize the hematopoietic response to Methylcobalamin, vitamin B12 through interference with erythrocyte maturation. Chloramphenicol is known to cause bone marrow suppression, especially when serum concentrations exceed 25 mcg/ml. Chloramphenicol should be discontinued if anemia attributable to chloramphenicol is noted during periodic blood studies, which should be done approximately every 2 days during chloramphenicol receipt. Aplastic anemia and hypoplasticanemiaare known to occur after chloramphenicol administration. Peripherally, pancytopenia is most often observed, but only 1—2 of the major cell types (erythrocytes, leukocytes, platelets) may be depressed in some cases.
- Metformin may result in suboptimal oral vitamin B12 absorption by competitively blocking the calcium-dependent binding of the intrinsic factor-vitamin B12 complex to its receptor. The interaction very rarely results in a pernicious anemia that appears reversible with discontinuation of metformin or with Methylcobalamin, vitamin B12 supplementation. Certain individuals may be predisposed to this interaction. Regular measurement of hematologic parameters is recommended in all patients on chronic metformin treatment; abnormalities should be investigated.
- Medications known to cause bone marrow suppression (e.g., myelosuppressive antineoplastic agents) may result in a blunted or impeded response to methylcobalamin, vitamin B12 therapy. Antineoplastic that are antimetabolites for the vitamin may induce inadequate utilization of vitamin B12. However, cancer patients usually benefit from vitamin B12 supplementation. The use of methotrexate may additionally invalidate diagnostic assays for folic acid and vitamin B12; however, this is a diagnostic laboratory test interference and not a drug interaction.
- The intranasal forms of methylcobalamin, vitamin B12, should be administered at least 1 hour before or 1 hour after ingestion of hot food or liquids. Hot foods may cause nasal secretions and a resulting loss of medication or medication efficacy. Interactions between foods and oral or injectable forms of methylcobalamin are not expected.
- Depressed levels of methylcobalamin, vitamin B12, and abnormal Schilling's test have been reported in patients receiving octreotide.
- The use of anti-infective agents or pyrimethamine may invalidate diagnostic assays for folic acid and vitamin B12; however, these are diagnostic laboratory test interferences and not true drug interactions.
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STORAGE AND INSTRUCTIONS:

Store between 15-25°C.

Protect from heat, sunlight & moisture.

Keep away from the reach of children.

To be sold on the prescription of a registered medical practitioner only.

HOW SUPPLIED

MOBICOL Injection 500mcg/ml

1ml x 10's ampoules

MOBICOL Tablet 500mcg

20's, 30's, 100's, 20x10's tablets.

خوراک وطریقہ استعمال:

ڈاکٹر کی ہدایت کے مطابق استعمال کریں۔

ہدایات:

دوا کو ۱۵-۲۵ ڈگری سینٹی گریڈ درجہ حرارت کے درمیان رکھیں۔

دھوپ، گرمی اور نمی سے بچائیں۔ بچوں کی پہنچ سے دور رکھیں۔

صرف رجسٹرڈ ڈاکٹر کے نسخے کے مطابق فروخت کریں۔

Manufactured by:

PHARMASOL PRIVATE LIMITED

Plot # 549, Sundar Industrial Estate, Lahore, Pakistan.