

Not to be sold by retail without the prescription of a Registered Medical Practitioner

Methylcobalamin, Pyridoxine Hydrochloride, Nicotinamide and Folic Acid
Injection
MEGO[®]-XL+ Injection

COMPOSITION

Each 2 ml contains:

Methylcobalamin IP	1000 mcg.
Pyridoxine Hydrochloride IP	100 mg.
Nicotinamide IP	100 mg.
Folic Acid IP	0.7 mg.
Benzyl Alcohol IP (as preservative)	2% w/v.
Water for Injections IP	q.s.

DOSAGE FORM

Injection.

INDICATIONS

MEGO-XL+ Injection is indicated for the treatment of peripheral neuropathies including diabetic neuropathy in adult patients.

DOSE AND METHOD OF ADMINISTRATION

Adults: The usual dosage is 1 ampule of MEGO-XL+ Injection daily, administered I.M. or I.V. infusion 3 times a week. The dosage may be adjusted depending on the patient's age and symptoms. Injectable therapy is usually given for 4 to 8 consecutive weeks; followed by, therapy can be continued with oral preparations.

Or, as prescribed by the Physician.

Direction / Handling Conditions

I.M. Administration: Following cautions should be exercised to avoid adverse effects on tissues or nerves. Avoid repeated injection at the same site. Do not inject in densely innervated site. 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.

I.V. Administration: MEGO-XL+ Injection should not be given as a direct, undiluted I.V. injection as it may give rise to dizziness, fainting, and possible tissue irritation. MEGO-XL+ Injection must be diluted prior to I.V. administration with a suitable/compatible diluent such as dextrose, saline or similar I.V. infusion solutions. The solution should be used within 4 hours after dilution. Intravenous infusion may be administered over a period of at least 30 minutes.

Pharmaceutical Precautions

Each ampoule is for single use only. Methylcobalamin 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. The unused portion, if any, should be discarded.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Do not use if solution is not clear or has suspended matter. The diluted solution for infusion should not be used if crystals or precipitates are observed.

USE IN SPECIAL POPULATIONS

MEGO-XL+ Injection is generally not intended for use in pregnancy, lactation, and in children.

1. Pregnant Women

Pregnancy Category C. Adequate and well-controlled studies have not been done in pregnant women. This product can be administered during pregnancy only at the recommendation of the physician.

2. Lactating Women

Vitamin B12 is known to be excreted in human milk. Caution should be exercised when this product is administered to a nursing woman. Nursing mothers should not use this preparation unless clearly needed and recommended by physician.

3. Pediatric Patients

This product has not been studied in children and thus, not indicated for use in pediatric population.

4. Geriatric Patients

Generally, dose adjustment is not required in the geriatric population with normal body functions (provided there is no severe renal and/or hepatic impairment).

CONTRAINDICATIONS

MEGO-XL+ Injection is contraindicated in the following:

- Patients with known or suspected hypersensitivity to any component of the formulation.
- Not to be used in newly born or premature infants.
- An existing hypervitaminosis.

WARNINGS AND PRECAUTIONS

Test Dose: Before therapy with MEGO-XL+ Injection is instituted, a test dose is recommended to ascertain possibility of hypersensitivity to ingredients of MEGO-XL+ Injection. Serious acute hypersensitivity reactions may require the use of subcutaneous epinephrine and other emergency measures.

Allergic Reactions: Use caution in the management of patients with known anaphylactic reactions to hydroxocobalamin or cyanocobalamin or methylcobalamin. Consideration should be given to use of alternative therapies, if available. Allergic reactions may include anaphylaxis, chest tightness, edema, angioneurotic edema, urticaria, pruritus, dyspnea, and rash.

Immune Response: Antibodies to hydroxocobalamin-transcobalamin II complex have developed during hydroxocobalamin therapy. Arrhythmias secondary to hypokalaemia have occurred at the beginning of parenteral treatment with hydroxocobalamin. This may happen with methylcobalamin therapy also.

Photolysis: Methylcobalamin 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 ampules to direct light.

Renal and Hepatic Impairment: This product has not been studied in hepatic and renal impairment patients. It is recommended to monitor renal and hepatic functions while patient is on this therapy.

DRUG INTERACTIONS

Methylcobalamin

Oral Contraceptives: Serum concentrations of methylcobalamin may be decreased by use of oral contraceptives.

Chloramphenicol: Chloramphenicol should not be used with methylcobalamin. Parenteral chloramphenicol may attenuate the effect of vitamin B12 in anemia.

Other Drugs: Metformin, H2 receptor antagonists (cimetidine, ranitidine etc.), aminoglycosides, colchicine, aminosalicic acid, anticonvulsants and alcohol decrease absorption of vitamin B12.

Drug/Laboratory Test Interactions: Persons taking most antibiotics, methotrexate, and pyrimethamine invalidate vitamin B12 diagnostic blood assays.

Pyridoxine

Pyridoxine reduces the effects of levodopa and activity of altretamine. It also decreases serum concentrations of phenobarbital and phenytoin. Pyridoxine may decrease antibiotic activities of erythromycin, kanamycin, streptomycin, doxycycline, and lincomycin. Drugs such as hydralazine, isoniazid, penicillamine, and oral contraceptives may increase the requirements for pyridoxine.

Nicotinamide

Nicotinamide may decrease antibiotic activities of erythromycin, kanamycin, streptomycin, doxycycline, and lincomycin.

Folic Acid

Phenytoin: Folic acid may increase phenytoin metabolism and lower the serum concentration of phenytoin resulting in increased seizure activity. Also, phenytoin may decrease serum folic acid concentrations.

Methotrexate: Folic acid may decrease a patient's response to methotrexate therapy.

Barbiturates: Folate reduces serum barbiturate concentrations.

Other Drugs and Alcohol: Folate deficiency states may be produced by drugs such as antiepileptics, oral contraceptives, anti-tuberculosis drugs, alcohol, and folic acid antagonists such as methotrexate, pyrimethamine, triamterene, trimethoprim, and sulfonamides.

Drug/Laboratory Test Interactions: Persons taking most antibiotics, methotrexate and pyrimethamine invalidate folic acid diagnostic blood assays.

UNDESIRABLE EFFECTS

Methylcobalamin

Anaphylactic Reaction: Anaphylactic reaction 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.

Other Adverse Reactions: Hypersensitivity, rash, erythema, pruritus, dizziness, agitation, anxiety, headache, hot sensation, diaphoresis, and pain/induration at the site of intramuscular injection. Pulmonary oedema, congestive heart failure (CHF), peripheral vascular thrombosis, polycythemia vera (bone marrow disorder), mild transient diarrhea, itching, transitory exanthema, feeling of swelling of entire body have also been reported with parenteral vitamin B substances.

Pyridoxine

Side effects such as headache, nausea, drowsiness, paresthesia (numbness/tingling of arms/legs) have been reported with pyridoxine when taken in large doses for a long time.

Nicotinamide

Upset stomach, nausea, and diarrhea may occur.

Folic Acid

Gastrointestinal disturbances and allergic sensitization have been reported rarely with folic acid.

OVERDOSE

No overdose has been reported with this product. In the event of overdose, treatment should be symptomatic and supportive. Hemodialysis may be effective in such circumstance.

PHARMACODYNAMICS

Methylcobalamin

Methylcobalamin is the neurologically active form of vitamin B12. Methylcobalamin is useful to treat or correct various neurological defects such as neuropathies. In many cases, liver does not convert cyanocobalamin, the commonly available form of vitamin B12, into adequate amounts of methylcobalamin. Nutritional inadequacies, enzyme defects, and pathological changes to tissues

can all contribute to a reduced ability of the body to accomplish the synthesis of the active forms of vitamin B12 from cyanocobalamin. MEGO-XL+ Injection provides readymade form of vitamin B12 i.e., methylcobalamin to treat various types of neuropathies. Methylcobalamin is effective in a range of 500 mcg to 1500 mcg per dose.

Methylcobalamin regulates nerve function and reduces plasma homocysteine levels by following mechanisms:

1. Methylcobalamin promotes myelination (phospholipid synthesis): Methylcobalamin 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.

2. Methylcobalamin promotes axonal transport and axonal regeneration: Methylcobalamin 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.

3. Methylcobalamin is a kind of endogenous coenzyme B12: Methylcobalamin plays an important role in transmethylation as a coenzyme of methionine synthetase in the synthesis of methionine from homocysteine.

4. Methylcobalamin is well transported to nerve cell organelles, and promotes nucleic acid and protein synthesis: Methylcobalamin is better transported to nerve cell organelles than cyanocobalamin in rats. Also, methylcobalamin promotes nucleic acid and protein synthesis in rats more than cobamamide does.

Pyridoxine

Pyridoxine/vitamin B6, a water soluble vitamin, is involved principally in amino acid metabolism, but is also involved in carbohydrate and fat metabolism. Pyridoxine have role as a coenzyme in a wide variety of enzymes involved in cell growth and cell division.

High homocysteine level in the blood (hyperhomocysteinemia) is a risk factor for cardiovascular disease, blood clotting abnormalities, myocardial infarction (heart attack), and ischemic stroke. Pyridoxine alone or in combination with folic acid has been shown to be effective for lowering homocysteine levels.

Nicotinamide

Niacin/nicotinamide required for the synthesis of nicotinamide adenine dinucleotide (NAD⁺) and nicotinamide adenine dinucleotide phosphate (NADP⁺) enzymes present in the cytosol of most cell. The nicotinamide nucleotides play a widespread role as coenzymes to many dehydrogenase enzymes occurring both in the cytosol and within the mitochondria. They are therefore key components of many metabolic pathways affecting carbohydrate, lipid, and amino acid metabolism. Generally, NAD⁺ linked dehydrogenases catalyze oxidoreduction reactions in

oxidative pathways, whereas NADP⁺ linked dehydrogenases or reductases are often found in pathways concerned with reductive syntheses.

Folic Acid

Folic acid is reduced in the body to tetrahydrofolate, which is a coenzyme for various metabolic processes including the synthesis of purine and pyrimidine nucleotides, and hence the synthesis of DNA. It is also involved in some amino-acid conversions, and in the formation and utilization of formate. Folic acid is used in the treatment and prevention of the folate deficiency state.

PHARMACOKINETICS

Methylcobalamin

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 diffuses across the placenta and also appears in breast milk. Vitamin B12 is stored in the liver, 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.

Pyridoxine

Pyridoxine crosses the placenta and is distributed into breast milk. Pyridoxine is stored mainly in the liver where there is oxidation to 4-pyridoxic acid and other inactive metabolites which are excreted in the urine. As the dose increases, proportionally greater amounts are excreted unchanged in the urine.

Nicotinamide

Nicotinamide and nicotinic acid are widely distributed in the body tissues. Nicotinic acid appears in breast milk. The main route of metabolism is their conversion to N-methylnicotinamide and the 2-pyridone and 4-pyridone derivatives; nicotinuric acid is also formed. Small amounts of nicotinic acid and nicotinamide are excreted unchanged in urine after therapeutic doses; however the amount excreted unchanged is increased with larger doses.

Folic Acid

Folic acid is converted to the metabolically active form 5-methyltetrahydrofolate in the plasma and liver. Folate is distributed into breast milk. The principal storage site of folate is the liver; it is also actively concentrated in the CSF. Folate undergoes enterohepatic circulation. Folate metabolites are eliminated in the urine and folate in excess of body requirements is excreted unchanged in the urine.

INCOMPATIBILITY

MEGO-XL+ Injection should not be mixed with any calcium containing preparation as folic acid content of this formulation is unstable in the presence of calcium salts such as calcium gluconate. MEGO-XL+ Injection should not be mixed with any other solution/injection for which physical and chemical compatibility has not been established.

SHELF-LIFE

Expiry date as mentioned on the product pack.

PACKAGING INFORMATION

2 ml glass ampoule.

STORAGE AND HANDLING INSTRUCTIONS

Store at a temperature not exceeding 25°C. Protect from light.

Keep out of reach of children.

Last updated: March 2020.