**SEREBAL**
(Mecobalamin)

500 mcg

Tablet

**COMPOSITION**

Each tablet contains:
Mecobalamin ..... 500mcg

**THERAPEUTIC INDICATIONS**

Indicated for the treatment of:

Peripheral neuropathies.
Megaloblastic anemia caused by vitamin $B_{12}$ deficiency.

**DOSAGE AND ADMINISTRATION**

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

**Method of Administration:**

MECOBALAMIN 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.
Intramuscular administration: In intramuscular administration, caution should be exercised, by following the instructions mentioned as follows to avoid adverse effects on tissues or nerves: Avoid repeated injection at the same site. Particular caution should be exercised when administering MECOBALAMIN to premature, neonates, nursing infants and children. 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.

**CONTRAINDICATIONS**

Hypersensitivity to the active substance or to any of the excipients

**SPECIAL WARNINGS AND PRECAUTIONS FOR USE**

*Tablet: General:* Mecobalamin should not be administered for extensive periods (months) to patients who show no clinical response. Prolonged use of larger doses of Mecobalamin is not recommended for patients whose occupation requires handling mercury or its compounds.
*Injection:* MECOBALAMIN should not be used aimlessly for more than one month unless it is effective.

**DRUG INTERACTIONS**

Absorption may be reduced by Para-aminosalicylic acid, colchinine, biguanides, neomycin, cholestyramine, potassium chloride, methyldopa, and cimetidine.

Patients treated with chloramphenicol may respond poorly to this medicine.

Serum levels of this medicine may be lowered by oral contraceptives

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

**FERTILITY, PREGNANCY AND LACTATION**

There are no data available for mecobalamin to be used in pregnant and lactating women

**EFFECTS ON ABILITY TO DRIVE AND USE MACHINES**

None**.**

**ADVERSE DRUG REACTIONS**

*With tablets Most commonly reported Adverse reactions are anorexia, nausea, vomiting and diarrhea. Rash occurs in less than 0.1% cases.*

*With Injection rash, hot sensation & headache occurs less than 0.1%. Diaphoresis and pain occur at the site of injection.*

Clinically significant adverse reactions (incidence unknown): *Anaphylactoid reactions:* Anaphylactoid reactions, 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.

**Reporting of suspected adverse reactions**

Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at pv@searlecompany.com

**OVERDOSE**

Experience to date with deliberate or accidental overdose is limited. No specific antidote is known. As in any case of overdose, treatment should be symptomatic and general supportive measures should be utilised

**PHARMACOLOGICAL PROPERTIES**

**Pharmacodynamic properties**

Pharmacotherapeutic group: Belongs to the class of vitamin B12 (cyanocobalamin and analogues). Used in the treatment of anemia.

ATC code: B03BA01

**Mechanism of action**

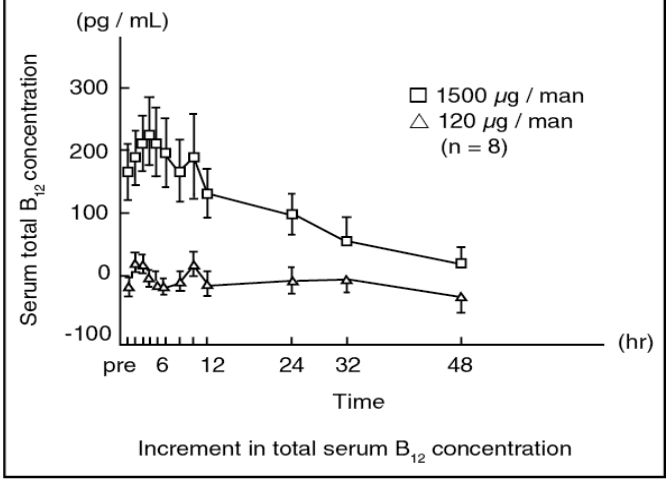
*Mecobalamin is a kind of endogenous coenzyme $B_{12}$:* Mecobalamin plays an important role in transmethylation as a coenzyme of methionine synthetase in the synthesis of methionine from homocysteine.
*Mecobalamin is well transported to nerve cell organelles, and promotes nucleic acid and protein synthesis:* 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.
*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.
*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.
*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.
*Injection: Mecobalamin promotes the maturation and division of erythroblasts, thereby alleviating anemia:* It is well known that vitamin $B_{12}$-deficiency may cause specific megaloblastic anemia. Mecobalamin promotes nucleic acid synthesis in bone marrow and promotes the maturation and

division of erythroblasts, thereby increasing erythrocyte production. Mecobalamin brings about a rapid recovery of diminished red blood cell, hemoglobin, and hematocrit in vitamin $B_{12}$-deficient rats.

**Pharmacokinetic properties**

*Tablet: Single dose administration:* When Mecobalamin 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 $\Delta AUC_0^{12}$ 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

**Figure 1.**




Increment in total serum $B_{12}$ concentration

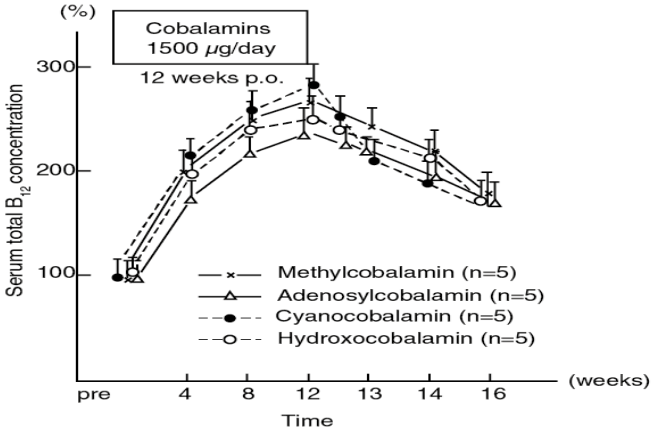
Table 3.

| Dose | $t_{max}$ (hr) | $C_{max}$ (pg/mL) | $\Delta C_{max}$ (pg/mL) | $\Delta C_{max}$ (%) | $\Delta AUC_0^{12*1}$ (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.

*Repeated dose administration:* Mecobalamin 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

**Figure 2.**

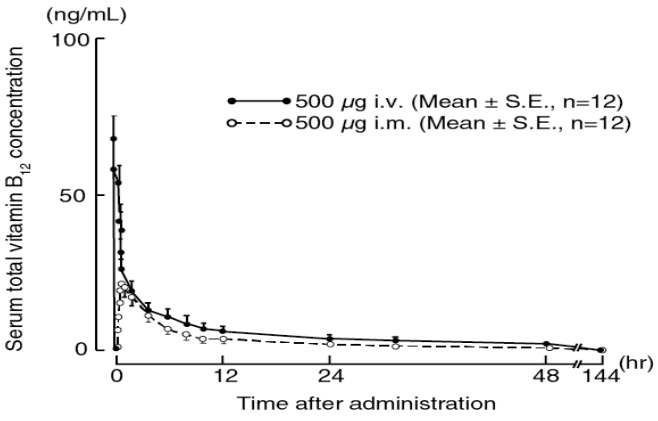



***Summary of Clinical Studies***

*Tablet:* 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.

*Injection:* Clinical efficacy: Mecobalamin was administered intramuscularly to patients with peripheral neuropathies in single doses of 500 μg and 100 μg (low-dose group) daily 3 times a week for 4 consecutive weeks in a double-blind clinical trial. In the chronic stage and fixed stage of peripheral neuropathies in the 500 μg group aggravation of symptoms was significantly suppressed compared to the low-dose group and this dose was thus demonstrated to be useful. In a placebo-controlled double-blind clinical trial, mecobalamin was administered intravenously or intramuscularly to patients with peripheral neuropathies at a single dose of 500 μg daily 3 times a week for 4 consecutive weeks. The improvement rate for intravenous administration was 38.7% (24/62) for moderately to remarkably improved and 74.2% (46/62) for fairly to remarkably improved. The improvement rate for intramuscular administration was 46.3% (25/54) for moderately to remarkably improved and 81.5% (44/54) for fairly to remarkably improved. The equivalence of mecobalamin efficacy for both administration routes was thus demonstrated. The diseases of subjects in the trial were diabetic neuropathy, polyneuritis, cervical spondylosis, sciatica, alcoholic neuropathy, facial paralysis and mononeuritis, etc.
When mecobalamin was administered to patients with megaloblastic anemia due to vitamin $B_{12}$ deficiency, their hemograms and symptoms improved in 3 weeks to 2 months after starting administration.

**Figure 3.**




Serum total vitamin $B_{12}$ concentration after single

*Repeated-dose administration:* Mecobalamin was administered intravenously to 6 healthy adult male volunteers at a single dose of 500 μg daily for 10 consecutive days. Serum total vitamin $B_{12}$ concentration determined before each administration increased from day to day. After 2 days of administration, the serum total vitamin $B_{12}$ concentration was 5.3±1.8ng/mL, about 1.4 times the 24 hr value (3.9±1.2ng/mL) after administration. At 3 days of administration it had increased to 6.8±1.5ng/mL, about 1.7 times the 24 hr value, and this concentration was maintained until the last dosing.

**PRECLINICAL SAFETY DATA**

No further relevant data.

**PRESENTATION**

Serebal 500mcg tablets are available in Alu-Alu blister pack of 2x10's.

**INSTRUCTIONS**

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

- Protect from sunlight, moisture and heat.

- Store below 30°C.

- Keep all medicines out of sight & reach of children.

**REGISTRATION NUMBER**

Serebal 500mcg Tablets :049425

Manufacturing License Number :000590

**NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION – As per registrations letter**

Mfg. NovaMed Specs. Manufactured by:

NovaMed Pharmaceuticals (Pvt.) Ltd.

28 Km, Ferozepur Road, Lahore-Pakistan.

Marketed by:

The Searle Company Limited,

One IBL Centre, 2nd Floor, Plot # 1,

Block 7 & 8, D.M.C.H.S, Tipu Sultan Road, Off Shahra-e-Faisal, Karachi - Pakistan.

**DATE OF PUBLICATION OF THE PACKAGE INSERT**

May 2021

SPL/SPC-SER.I/521-000(001)