# Tonext®

(As per Innovator's Specification)
**(Mecobalamin)**
(JP Specification)
**500**mcg Capsules

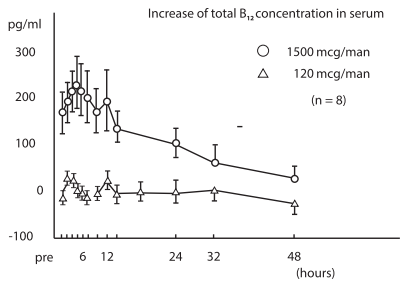
**COMPOSITION**
**TONEXT** 500mcg Capsules:
Each capsule contains:
Mecobalamin ..... 500mcg
(As per Innovator's Specification)

**DESCRIPTION**
**TONEXT** is a mecobalamin preparation for the treatment of peripheral neuropathies. **TONEXT** contains mecobalamin, a vitamin $B_{12}$-coenzyme that occurs in the blood and the cerebrospinal fluid; it is taken up by nerve tissues more actively and extensively than other homologues of vitamin $B_{12}$. Biochemically, **TONEXT** promotes the metabolic pathways of nucleic acids, proteins and lipids through its involvement in the transmethylation reaction; thus, it exerts a repairing effect on injured nerve tissues. Clinically, **TONEXT** is the pharmaceutical product that has been shown, by double- blind clinical trials, to be effective and useful for the treatment of numbness, pain and paralysis due to peripheral neuropathies such as diabetic neuropathy and polyneuritis.

**CLINICAL PARTICULARS**
**Indication:**
Peripheral neuropathies
**Dosage and Administration:**
The usual adult dosage for oral use is 3 Capsules (1,500mcg of mecobalamin) daily in three divided doses.
The dosage may be adjusted depending on the patient's age and symptoms.
**Precautions:**
**TONEXT** should not be used for more than one month unless it is effective. Prolonged use of larger doses of **TONEXT** is not recommended for patients whose occupation requires handling mercury or its compounds.
**Adverse Reactions:**
(rarely : <0.1%, infrequently: 0.1%-<5%, no specific designation: ≥5% or frequency unknown).
*Gastrointestinal:* Symptoms such as anorexia, nausea or diarrhoea may infrequently occur.
*Hypersensitivity:* Rash may occur rarely.

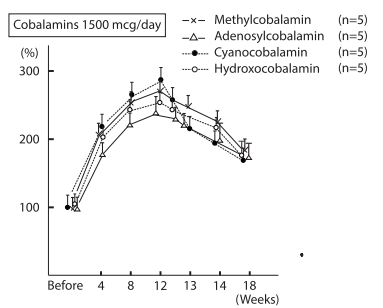
**CLINICAL PHARMACOLOGY**
**Pharmacokinetics:**
*1. Single dose administration:* After oral administration of single doses of 120mcg or 1,500mcg* of mecobalamin to healthy adult volunteers dose-dependent peak plasma concentrations were reached in 3 hours in both cases. The half-life, increase of the serum concentration of total vitamin $B_{12}$ and $AUC_0^{12}$ are shown in the following figure and table.

Of the cumulative amount of total $B_{12}$ recovered in the urine by 24 hours after oral administration, 40 to 80 percent was excreted within the first 8 hours. Note: The single dose of 1,500mcg marked with symbol* are unapproved.




| Dose | t max (hour) | C max (pg/ml) | △cmax (pg/ml) | △cmax (%) | $\triangle AUC_0^{12}$ [1] (hour. pg/ml) | t 1/2[2] (hour) |
|---|---|---|---|---|---|---|
| 120 mcg | 2.8 ± 0.2 | 743 ± 47 | 37 ± 35 | 5.1 ± 2.1 | 168 ± 58 | N.A. |
| 1500 mcg | 3.6 ± 0.5 | 972 ± 55 | 255 ± 51 | 36.0 ± 7.9 | 2033 ± 510 | 12.5 |

1) Calculated by the trapezoidal formula from the increment in observed 12- hour values, as compared to pre-drug values.
2) Calculated from the average of 24-48 hour values. Mean ± Standard error
*2. Repeated dose administration:* Serum concentrations of total $B_{12}$ were measured in healthy adult volunteers given an oral daily dose of 1,500mcg of **TONEXT** for 12 consecutive weeks. Serum $B_{12}$ concentrations were also monitored in the same patients for 4 weeks immediately following the last administration. The serum concentration increased for the first 4 weeks after administration, reaching a value twice as high as the initial concentration. Thereafter, there was a gradual increase which reached a peak at approximately 280% of the initial value at the 12th week of dosing. The serum concentration declined after the last administration (12 weeks), but was still approximately 180% of the initial level 4 weeks after the last administration.




**Pharmacodynamics:**
*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 plays the role of a coenzyme in the synthesis of methionine from homocysteine. It has been shown in experiments with cells of brain origin and spinal nerve cells to be concerned in the synthesis of thymidine from deoxyuridine in promoting nucleic acid and

protein synthesis.

*Mecobalamin promotes axonal transport of skeletal protein and axonal regeneration:* Mecobalamin normalizes axonal transport of skeletal protein in sciatic nerve cells from rats 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 myclination (phospholipid synthesis):* Mecobalamin promotes the synthesis of lectithin, the main constituent of medullary sheath lipid, by increasing methionine synthetase activity, thus promoting myelination.

*Mecobalamin restores delayed synaptic transmission and diminished neurotransmitters toward normal:* Mecobalamin restores end-plate potential induction early by increasing nerve fiber excitability in the crushed sciatic nerve (rats). In addition, mecobalamin normalizes diminished brain tissue levels of acetylcholine in rats fed a choline-deficient diet.

**Clinical Studies**

*Clinical efficacy:* In clinical studies, including double-blind clinical trials, Mecobalamin produced good or excellent relief of symptoms in 44.5% (5,503/12,373) of patients with peripheral neuropathies. In double-blind controlled comparative trials of mecobalamin with cobamamide (DBCC) or lower dose of mecobalamin (120 mcg), the efficacy and usefulness of mecobalamin to the patients with chronic and fixed symptoms were confirmed.

*Adverse reactions, including changes in laboratory values:* Out of 15,180 patients treated with mecobalamin, adverse reactions were reported in 146 patients (0.96%). The most common adverse reactions were gastrointestinal symptoms such as anorexia in 52 cases (0.34%), gastrointestinal disorders in 38 cases (0.25%), nausea-vomiting in 18 cases (0.12%), diarrhoea in 17 cases (0.11%), and rash in 14 cases (0.09%).

No changes in laboratory values have been attributed to mecobalamin treatment.

**Non-clinical studies**

*Distribution:* In rats given a 25mcg oral dose of Co-labelled mecobalamin, radioactivity was found to be higher in the kidneys, adrenal glands, pancreas, liver and stomach (listed in order of magnitude), whereas the muscles, testes, brain, and nerves did not show significant radioactivity 72 hours after administration.

*Single dose toxicity ($LD_{50}$ mg/kg):*

| Animal | p.o. |
|---|---|
| Mice | >1,000 |
| Rats | >500 |

*Repeated dose toxicity (1 month):* The oral administration of mecobalamin, at doses of 0.2, 2.0 or 20mg/kg/day to rats for 1 consecutive month, resulted in no remarkable changes in general condition of the animals, body weights, blood and urine analytical results, organ weights, or histopathological findings.

*Repeated dose toxicity (6 months):* In rats given oral doses of 0.2, 2.0 or 20mg/kg/day of mecobalamin for 6 consecutive months, no remarkable changes were noted in general condition of the animals, body weights, blood and urine analytical results, organ weights, or histopathological findings.

*Reproductive and developmental toxicity:* In mature nulliparous mice and rats, given oral doses of 0.2, 2.0 or 20mg/kg/day of mecobalamin during the period of organogenesis, no abnormalities or signs of teratogenicity were noted in fetuses or neonates.

*Methylation of inorganic mercury:* In vitro, a chemical reaction occurs such that mecobalamin forms methyl mercury with mercuric chloride. This reaction, however, doses not take place in the presence of proteins as in the human blood.

Experiments with rats fed a diet containing inorganic mercury have shown clearly that oral administration of mecobalamin does not increase the formation of methyl mercury in the body. In male rats fed a diet containing inorganic mercury, mecobalamin administered in oral doses of 1.5 and 15mg/kg/day for 6 consecutive months did not affect the general condition of the animals, and no toxic sign were observed with urinalysis nor from hematological or histopathological examinations.

**STORAGE**

Store below 30°C. Protect from light and moisture.

**HOW SUPPLIED**

**TONEXT** 500mcg Capsules: Pack of 14's capsules.

**TO BE SOLD ON THE PRESCRIPTION OF A REGISTERED MEDICAL PRACTITIONER ONLY.**

**KEEP ALL MEDICINES OUT OF THE REACH OF CHILDREN.**

Lactose & Gluten Free

# ٹونیکسٹ

## (میکوبالامن)

## 500 مائیکروگرام

## کیپسولز

### خوراک وہدایات

ڈاکٹر کی ہدایات کے مطابق استعمال کریں۔

صرف مستند ڈاکٹر کے نسخہ کے مطابق ہی دوا فروخت کی جائے۔

تمام ادویات بچوں کی پہنچ سے دور رکھیں۔

دوا کو 30°C سے کم درجہ حرارت پر، نمی اور روشنی سے محفوظ رکھیں۔

NEXT PHARMACEUTICAL

Manufactured by:
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