For the use of a Registered Medical Practitioner or a Hospital or a Laboratory only

CARNISURE PLUS

1. Generic Name

Methylcobalamin, Folic acid and Levocarnitine Tablets

2. Qualitative and quantitative Composition:

Each film-coated tablet contains:

Levocarnitine U.S.P. ……. 250 mg

Mecobalamin I.P. ……. 1500 mcg

(Methylcobalamin)

Folic Acid I.P. ……. 1.5 mg

Colours: Red Oxide of Iron & Titanium Dioxide I.P.

Appropriate overages of vitamins added to compensate for loss on storage.

Excipients are used microcrystalline cellulose, Povidone, isopropyl alcohol, magnesium stearate, colloidal silicon dioxide, ethyl cellulose, methylene chloride, Instamoist shield.

3. Dosage form and strength

Dosage form: Tablets

Strength: Levocarnitine 250 mg, Mecobalamin. 1500 mcg and Folic Acid 1.5 mg

4. Clinical particulars

4.1. Therapeutic indication

Carnisure Plus is indicated as vitamin and micronutrient supplementation in the management of chronic disease.

4.2. Posology and method of administration

Posology

As directed by physician.

Method of administration

For oral administration only.

4.3. Contraindications

- Hypersensitivity to the active substance or to any of the excipients.

4.4. Special warnings and precautions for use

L-Carnitine

The safety and efficacy of oral L-Carnitine has not been evaluated in patients with renal insufficiency. Chronic administration of high doses of oral L-Carnitine in patients with severely compromised renal function or in ESRD patients on dialysis may result in accumulation of the potentially toxic metabolites, trimethylamine (TMA) and Trimethylamine-N-oxide (TMAO), since these metabolites are normally excreted in the urine.

Mecobalamin

Should be given with caution in patients suffering from folate deficiency. The following warnings and precautions suggested with parent form – vitamin B12 The treatment of vitamin B12 deficiency can unmask the symptoms of polycythaemia vera. Megaloblastic anemia is sometimes corrected by treatment with vitamin B12. But this can have very serious side effects. Don't attempt vitamin B12 therapy without close supervision by healthcare provider. Do not take vitamin B12 if Leber's disease, a hereditary eye disease. It can seriously harm the optic nerve, which might lead to blindness.

Folic acid

Administration of folic acid alone is improper therapy for pernicious anemia and other megaloblastic anemias in which vitamin B12 is deficient. Folic acid in doses above 0.1 mg daily may obscure pernicious anemia in that hematologic remission can occur while neurologic manifestations remain progressive. There is a potential danger in administering folic acid to patients with undiagnosed anemia since folic acid may obscure the diagnosis of pernicious anemia by alleviating the hematologic manifestations of the disease while allowing the neurologic complications to progress. This may result in severe nervous system damage before the correct diagnosis is made. Adequate doses of vitamin B12 may prevent, halt, or improve the neurologic changes caused by pernicious anemia.

Carnisure Plus tablets are highly hygroscopic in nature. Exposure to open/humid conditions may moist the tablets affecting their shape and appearance. Hence do not keep the tablets open.

4.5. Drugs interactions

L-Carnitine

Reports of INR increase with the use of warfarin-like products have been observed. INR levels should be monitored.

Mecobalamin

The data are unavailable for Mecobalamin drug interaction, however evidence for parent drug vitamin B12 are as follows; Absorption from the gastrointestinal tract may be reduced by neomycin, amino salicylic acid, histamine H2-antagonists, omeprazole, and colchicine. Serum concentrations may be decreased by use of 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. Parenteral chloramphenicol may attenuate the effect in anaemia. Potassium supplements can reduce absorption of vitamin B12 in some people and might contribute to vitamin B12 deficiency. Folic acid, particularly in large doses, can cover up vitamin B12 deficiency, and cause serious health effects. Be sure that healthcare provider checks vitamin B12 levels before start of folic acid. Early research suggests that vitamin C supplements can destroy dietary vitamin B12. It isn't known whether this interaction is important, but to stay on the safe side, take vitamin C supplements at least 2 hours after meals. Heavy drinking for at least a two-week period can decrease vitamin B12 absorption from the gastrointestinal tract.

Folic acid

There is evidence that the anticonvulsant action of phenytoin is antagonized by folic acid. A patient whose epilepsy is completely controlled by phenytoin may require increased doses to prevent convulsions if folic acid is given. Folate deficiency may result from increased loss of folate, as in renal dialysis and/or interference with metabolism (e.g. folic acid antagonists such as methotrexate); the administration of anticonvulsants, such as diphenylhydantoin, primidone, and barbiturates; alcohol consumption and, especially alcoholic cirrhosis; and the administration of pyrimethamine

and nitrofurantoin. False low serum and red cell folate levels may occur if the patient has been taking antibiotics, such as tetracycline, which suppress the growth of Lactobacillus casei.

4.6. Use in special populations (such as pregnant women, lactating women, paediatric patients, geriatric patients etc.)

L-Carnitine

Reproductive studies have been performed in rats and rabbits at doses up to 3.8 times the human dose on the basis of surface area and have revealed no evidence of impaired fertility or harm to the fetus due to L-Carnitine. There are, however, no adequate and well controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

L-Carnitine supplementation in nursing mothers has not been specifically studied. Studies in dairy cows indicate that the concentration of L-Carnitine in milk is increased following exogenous administration of L-Carnitine. In nursing mothers receiving L-Carnitine, any risks to the child of excess carnitine intake need to be weighed against the benefits of L-Carnitine supplementation to the mother. Consideration may be given to discontinuation of nursing or of L-Carnitine treatment.

Mecobalamin

No data available for use of Mecobalamin in special population.

Folic acid

Folic acid is usually indicated in the treatment of megaloblastic anemias of pregnancy. Folic acid requirements are markedly increased during pregnancy, and deficiency will result in fetal damage. Studies in pregnant women have not shown that folic acid increases the risk of fetal abnormalities if administered during pregnancy. If the drug is used during pregnancy, the possibility of fetal harm appears remote. Because studies cannot rule out the possibility of harm, however, folic acid should be used during pregnancy only if clearly needed. Folic acid is excreted in the milk of lactating mothers. During lactation, folic acid requirements are markedly increased; however, amounts present in human milk are adequate to fulfil infant requirements, although supplementation may be needed in low birth-weight infants, in those who are breast-fed by mothers with folic acid deficiency (50µg daily), or in those with infections or prolonged diarrhea

4.7. Effects on ability to drive and use machines

There are no data the effect of this product on driving capacity and use of machines. An effect is, however, unlikely.

4.8. Undesirable effects

L-Carnitine

Various mild gastrointestinal complaints have been reported during the long-term administration of oral L-carnitine (also with D, L-carnitine); these include transient nausea and vomiting, abdominal cramps, and diarrhea. Mild myasthenia has been described only in uremic patients receiving D, L-carnitine. Decreasing the dosage often diminishes or eliminates drug-related patient body odour or gastrointestinal symptoms when present. Tolerance should be monitored very closely during the first week of administration, and after any dosage increases. Seizures have been reported to occur in patients with or without pre-existing seizure activity receiving either oral or intravenous L-Carnitine. In patients with pre-existing seizure activity, an increase in seizure frequency and/or severity has been reported.

Mecobalamin.

- Pulmonary edema and congestive heart failure early in treatment; peripheral vascular thrombosis.

- Polycythemia vera may also be seen.
- Mild transient diarrhea has been seen.
- Rarely itching; transitory exanthema.

Other adverse effects reported with vitamin B12 are diarrhea, blood clots, itching, serious allergic reactions.

Folic acid

Allergic sensitization has been reported following both oral and parenteral administration of folic acid. Folic acid is relatively nontoxic in man. Rare instances of allergic responses to folic acid preparations have been reported and have included erythema, skin rash, itching, general malaise, and respiratory difficulty due to bronchospasm. One patient experienced symptom suggesting anaphylaxis following injection of the drug. Gastrointestinal side effects, including anorexia, nausea, abdominal distention, flatulence, and a bitter or bad taste, have been reported in patients receiving 15 mg folic acid daily for 1 month. Other side effects reported in patients receiving 15 mg daily include altered sleep patterns, difficulty in concentrating, irritability, over activity, excitement, mental depression, confusion, and impaired judgment. Decreased vitamin B12 serum levels may occur in patients receiving prolonged folic acid therapy. In an uncontrolled study, orally administered folic acid was reported to increase the incidence of seizures in some epileptic patients receiving phenobarbital, primidone, or diphenylhydantoin. Another investigator reported decreased diphenylhydantoin serum levels in folate-deficient patients receiving diphenylhydantoin who were treated with 5 mg or 15 mg of folic acid daily.

Reporting of adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Report suspected adverse reactions via any point of contact available at www.torrentpharma.com.

4.9. Overdose

L-Carnitine

There have been no reports of toxicity from L-Carnitine overdosage. L-Carnitine is easily removed from plasma by dialysis. The intravenous LD50 of L-Carnitine in rats is 5.4 g/kg and the oral LD50 of L-Carnitine in mice is 19.2 g/kg. Large doses of L-Carnitine may cause diarrhea.

Mecobalamin

Evidence is unavailable for overdose of Mecobalamin. Folic acid Except during pregnancy and lactation, folic acid should not be given in therapeutic doses greater than 0.4 mg daily until pernicious anemia has been ruled out. Patients with pernicious anemia receiving more than 0.4 mg of folic acid daily who are inadequately treated with vitamin B12 may show reversion of the hematologic parameters to normal, but neurologic manifestations due to vitamin B12 deficiency will progress.

Folic acid

Doses of folic acid exceeding the Recommended Dietary Allowance (RDA) should not be included in multivitamin preparations; if therapeutic amounts are necessary, folic acid should be given separately.

5. Pharmacological properties

5.1. Mechanism of Action

Levocarnitine

Levocarnitine can be synthesized within the body from the amino acids lysine or methionine. Vitamin C (ascorbic acid) is essential to the synthesis of carnitine. Levocarnitine is a carrier molecule in the transport of long chain fatty acids across the inner mitochondrial membrane. It also exports acyl groups from subcellular organelles and from cells to urine before they accumulate to toxic concentrations. Only the L isomer of carnitine (sometimes called vitamin BT) affects lipid metabolism. Levocarnitine is handled by several proteins in different pathways including carnitine transporters, carnitine translocases, carnitine acetyltransferases and carnitine palmitoyltransferases.

Mecobalamin

Methylcobalamin is the form of vitamin B12 active in the central nervous system. It is essential for cell growth and replication. In some people the liver may not convert cyanocobalamin, the common supplemental form of vitamin B12, into adequate amounts of Methylcobalamin needed for proper neuronal functioning. Methylcobalamin may exert its neuroprotective effects through enhanced methylation, acceleration of nerve cell growth, or its ability to maintain already healthy homocysteine levels.

Folic Acid

Folic acid (also known as vitamin B9) is very important for the development of a healthy foetus, as it can significantly reduce the risk of neural tube defects (NTDs), such as spina bifida. People can get folic acid deficiency anemia if they do not eat enough foods which contain folic acid, they require higher quantities of it and are not taking them, such as pregnant and lactating women, individuals with medical problems, such as sickle cell disease, or the person's body does not absorb enough of it, as may happen with alcohol abuse or improper functioning kidneys.

5.2. Pharmacodynamic properties

L-carnitine:

L-carnitine is a naturally occurring substance required in mammalian energy metabolism. It has been shown to facilitate long-chain fatty acid entry into cellular mitochondria, thereby delivering substrate for oxidation and subsequent energy production. Fatty acids are utilized as an energy substrate in all tissues except the brain. In skeletal and cardiac muscle, fatty acids are the main substrate for energy production. Primary systemic carnitine deficiency is characterized by low concentrations of L-Carnitine in plasma, RBC, and/or tissues. It has not been possible to determine which symptoms are due to carnitine deficiency and which are due to an underlying organic acidemia, as symptoms of both abnormalities may be expected to improve with L-Carnitine tablet. The literature reports that carnitine can promote the excretion of excess organic or fatty acids in patients with defects in fatty acid metabolism and/or specific organic acidopathies that bioaccumulate acylCoA esters. Secondary carnitine deficiency can be a consequence of inborn errors of metabolism. L-Carnitine tablet may alleviate the metabolic abnormalities of patients with inborn errors that result in accumulation of toxic organic acids. Conditions for which this effect has been demonstrated are: glutaric aciduria II, methyl malonic aciduria, propionic acidemia, and medium chain fatty acylCoA dehydrogenase deficiency. Autointoxication occurs in these patients due to the accumulation of acylCoA compounds that disrupt intermediary metabolism. The subsequent hydrolysis of the acylCoA compound to its free acid results in acidosis which can be life-threatening. L-Carnitine clears the acylCoA compound by formation of acylcarnitine, which is quickly excreted. Carnitine deficiency is defined biochemically as abnormally low plasma concentrations of free carnitine, less than 20 µmol/L at one-week post term and may be associated with low tissue and/or urine concentrations. Further, this condition may be associated with a plasma concentration ratio of acylcarnitine/LCarnitine greater than 0.4 or abnormally elevated

concentrations of acylcarnitine in the urine. In premature infants and newborns, secondary deficiency is defined as plasma L-Carnitine concentrations below age-related normal concentrations. Pharmacokinetic properties

Mecobalamin:

Mecobalamin is one of the biologically active forms of vitamin B12. It acts as coenzymes in nucleic acid synthesis. Mecobalamin is also closely involved with folic acid in several important metabolic pathways. Mecobalamin (CH3B12) supports the methionine synthetase reaction, which is essential for normal metabolism of folate.

Folic acid

Folic acid acts on megaloblastic bone marrow to produce a normoblastic marrow. In man, an exogenous source folate is required for nucleoprotein synthesis and the maintenance of normal erythropoiesis. Folic acid is the precursor of tetrahydrofolic acid, which is involved as a cofactor for transformylation reactions in the biosynthesis of purines and thymidylates of nucleic acids. Impairment of thymidylate synthesis in patients with folic acid deficiency is thought to account for the defective deoxyribonucleic acid (DNA) synthesis that leads to megaloblastic formation and megaloblastic and macrocytic anemias. Folic acid is absorbed rapidly from the small intestine, primarily from the proximal portion. Naturally occurring conjugated folates are reduced enzymatically to folic acid in the gastrointestinal tract prior to absorption. Folic acid appears in the plasma approximately 15 to 30 minutes after an oral dose; peak levels are generally reached within 1 hour. After intravenous administration, the drug is rapidly cleared from the plasma. Cerebrospinal fluid levels of folic acid are several times greater than serum levels of the drug. Folic acid is metabolized in the liver to 7,8-dihydrofolic acid and eventually to 5,6,7,8-tetrahydrofolic acid with the aid of reduced diphospho-pyridine nucleotide (DPNH) and folate reductases. Tetrahydrofolic acid is linked in the N5 or N10 positions with formyl, hydroxymethyl, methyl, or formimino groups. N5-formyltetrahydrofolic acid is leucovorin. Tetrahydrofolic acid derivatives are distributed to all body tissues but are stored primarily in the liver. Normal serum levels of total folate have been reported to be 5 to 15 ng/mL; normal cerebrospinal fluid levels are approximately 16 to 21 ng/mL. Normal erythrocyte folate levels have been reported to range from 175 to 316 ng/mL. In general, folate serum levels below 5 ng/mL indicate folate deficiency, and levels below 2 ng/mL usually result in megaloblastic anemia. After a single oral dose of a 100 µg of folic acid in a limited number of normal adults, only a trace amount of the drug appeared in the urine. An oral dose of 5 mg in 1 study and a dose of 40 µg/kg of body weight in another study resulted in approximately 50% of the dose appearing in the urine. After a single dose of 15 mg up to 90% of the dose was recovered in the urine. A majority of the metabolic products appeared in the urine after 6 hours; excretion was generally complete within 24 hours. Small amounts of orally administered folic acid have also been recovered in the feces. Folic acid is also excreted in the milk of lactating mothers.

5.3. Pharmacokinetic properties

L-Carnitine

In a relative bioavailability study in 15 healthy adult male volunteers, L-Carnitine tablet were found to be bio-equivalent to L-Carnitine oral solution. Following 4 days of dosing with 6 tablets of L-Carnitine tablet 330 mg b.i.d. or 2 g of L-Carnitine oral solution b.i.d., the maximum plasma concentration (Cmax) was about 80 µmol/L and the time to maximum plasma concentration (Tmax) occurred at 3.3 hours. The plasma concentration profiles of L-Carnitine after a slow 3-minute intravenous bolus dose of 20 mg/kg of L-Carnitine were described by a two-compartment model. Following a single I.V. administration, approximately 76% of the L-Carnitine dose was excreted in the urine during the 0-24h interval. Using plasma concentrations uncorrected for endogenous L-Carnitine, the mean distribution half-life was 0.585 hours, and the mean apparent terminal elimination half-life was 17.4 hours. The absolute bioavailability of L-Carnitine from the two oral

formulations of L-Carnitine, calculated after correction for circulating endogenous plasma concentrations of L-Carnitine, was 15.1 ± 5.3% for L-carnitine tablet and 15.9 ± 4.9% for L-Carnitine oral solution.

Total body clearance of L-Carnitine (Dose/AUC including endogenous baseline concentrations) was a mean of 4.00 L/h., L-Carnitine was not bound to plasma protein or albumin when tested at any concentration or with any species including the human.

In a pharmacokinetic study where five normal adult male volunteers received an oral dose of [3 Hmethyl]-L-carnitine following 15 days of a high carnitine diet and additional carnitine supplement, 58 to 65% of the administered radioactive dose was recovered in the urine and feces in 5 to 11 days. Maximum concentration of [3 H-methyl]-L-carnitine in serum occurred from 2.0 to 4.5 hr after drug administration. Major metabolites found were trimethylamine N-oxide, primarily in urine (8% to 49% of the administered dose) and [m 3 H]-γ-butyrobetaine, primarily in feces (0.44% to 45% of the administered dose). Urinary excretion of L-Carnitine was about 4 to 8% of the dose. Fecal excretion of total carnitine was less than 1% of the administered dose.

After attainment of steady state following 4 days of oral administration of L-Carnitine tablet (1980 mg q12h) or oral solution (2000 mg q12h) to 15 healthy male volunteers, the mean urinary excretion of L-Carnitine during a single dosing interval (12h) was about 9% of the orally administered dose (uncorrected for endogenous urinary excretion).

Mecobalamin

It binds to intrinsic factor; a glycoprotein secreted by the gastric mucosa and is 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. After intranasal dosage, peak plasma concentrations of cyanocobalamin have been reached in 1 to 2 hours. The bioavailability of the intranasal preparation is about 7 to 11% of that by intramuscular injection.

It is extensively bound to specific plasma proteins called trans cobalamins trans cobalamin II appears to be involved in the rapid transport of the cobalamins to tissues. A parent form -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. Vitamin B12 diffuses across the placenta and appears in breast milk.

Folic acid

Folic acid is rapidly absorbed from the gastrointestinal tract, mainly from the duodenum and jejunum. Dietary folates are stated to have about half the bioavailability of crystalline folic acid. The naturally occurring folate polyglutamates are largely deconjugated, and then reduced by dihydrofolate reductase in the intestines to form 5- methyltetrahydrofolate, which appears in the portal circulation, where it is extensively bound to plasma proteins. Folic acid given therapeutically enters the portal circulation largely unchanged, since it is a poor substrate for reduction by dihydrofolate reductase. It is converted to the metabolically active form 5- methyltetrahydrofolate in the plasma and liver. 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. Folate is distributed into breast milk. Folic acid is removed by haemodialysis.

6. Nonclinical properties

6.1. Animal Toxicology or Pharmacology

L-Carnitine

LD50 > 8g/kg (mouse, oral). Adverse effects include hypertension, fever, tachycardia, and seizures.

Mecobalamin

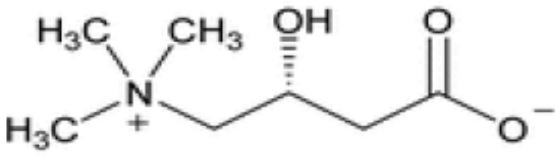
Not Available

Folic acid

Toxicity studies in animals (rats and rabbits) have shown that massive doses (100mg/kg upwards) produce precipitation of folate crystals in renal tubules, particularly proximal tubules, and ascending limb of the loop of Henle. Tubular necrosis is followed by recovery.

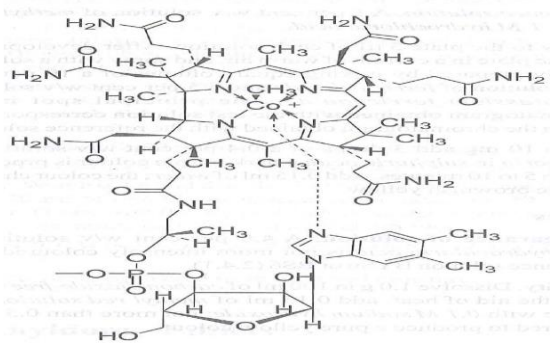
7. Description

Levocarnitine is (R)-3-Carboxy-2-hydroxy-*N*, *N*, *N*-trimethyl-1-propanaminium. Levocarnitine is a white crystals or crystalline powder. Hygroscopic. It is freely soluble in water, and in hot alcohol, practically insoluble in acetone, in ether, and in benzene. The molecular formula is $C_7H_{15}NO_3$ and the molecular weight is 161.20 g/mol. The structural formula is:



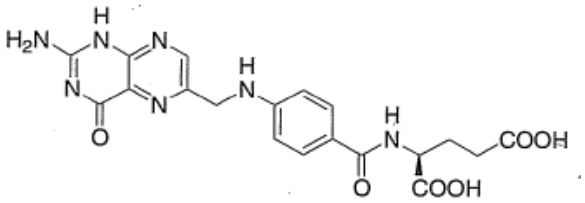
Mecobalamin

Mecobalamin is Coα- [α - (5, 6-dimethyl-1H-benzoimidazole-1-yl)]- Co-β-methylcobamide. Mecobalamin is a dark red crystalline powder. It is a sparingly Soluble in water, slightly soluble in ethanol and practically insoluble in acetonitrile. The molecular formula is $C_{63}H_{91}CoN_{13}O_{14}P$, HCl and the molecular weight is 1344.4 g/mol The structural formula is:



Folic Acid

Folic Acid is (2S)-[4-[(2-amino-4-hydroroxypteridin-6-yl) methylamino] benzamido] glutamic acid. Glimepiride is A yellow to yellowish-orange, crystalline powder, odourless or almost odourless. It is soluble in dilute acids and in alkaline solutions, very slightly soluble in boiling water, practically insoluble in cold water and in most organic solvents. The molecular formula is $C_{19}H_{19}N_7O_6$ and the molecular weight is 441.4 g/mol. The structural formula is:



CARNISURE PLUS is Brick red coloured, capsule shaped, film coated tablets. CARNISURE PLUS contains excipients are microcrystalline cellulose, Povidone, isopropyl alcohol, magnesium stearate, colloidal silicon dioxide, ethyl cellulose, methylene chloride, Instamoist shield.

8. Pharmaceutical particulars

8.1. Incompatibilities

Not applicable

8.2. Shelf-life

Do not use later than the date of expiry.

8.3. Packaging information

CARNISURE PLUS is available in Blister strip of 10 Tablets.

8.4. Storage and handing instructions

Store at temperature not exceeding 25° C in a dry place. Keep out of reach of children.

9. Patient Counselling Information

Ask the patients to inform the treating physicians in case of any of the below:

- Have any allergies
- Have kidney or liver problems
- Are pregnant or plan to become pregnant
- Are breastfeeding or plan to breastfeed
- Have any serious illness
- Are taking any medicines (prescription, over-the-counter, vitamins, or herbal products)

10. Details of manufacturer

Windlas Biotech Pvt. Limited (Plant-2),

Khasra No. 141-143 & 145, Mohabewala Industrial Area, Dehradun - 248 110, Uttarakhand

11. Details of permission or licence number with date

55/UA/SC/P-2013 issued on 15.01.2018

12. Date of revision

FEB 2026

MARKETED BY

TORRENT PHARMACEUTICALS LTD.

IN/Carnisure Plus/250mg,1500mcg,1.5mg/FEB-2026/03/PI