Product Summary

1. Name of the medicinal product
Gofolate Plus®

2. Qualitative and quantitative composition
Each film coated tablet contains:
Methylcobalamin 1500 mcg
L-Methylfolate calcium 1mg
Pyridoxal-5-Phosphate 0.5mg
Excipients q.s

3. Pharmaceutical form
Film coated tablet

4. Clinical particulars
4.1 Therapeutic indications
Gofolate Plus® tablets are indicated for the distinct nutritional requirements of patients with endothelial dysfunction\textsuperscript{11-13} who present with loss of protective sensation\textsuperscript{14} and neuropathic pain\textsuperscript{15-17} associated with diabetic peripheral neuropathy. Gofolate Plus® tablets are indicated for the distinct nutritional requirements of patients with endothelial dysfunction and/or hyperhomocysteinemia\textsuperscript{18} who present with lower extremity ulceration(s).\textsuperscript{19-21}

4.2 Posology and method of administration
Gofolate Plus® must be used under medical supervision.

4.3 Contraindications
There have been rare reports of hypersensitivity (allergic-like reactions) to
GofolatePlus®. Therefore, a known hypersensitivity to any of the components in the product is a contraindication to its use for any indication.

4.4 Special warnings and precautions for use

**General**

Folic acid, when administered as a single agent in doses above 0.1mg daily, may obscure the detection of B12 deficiency (specifically, the administration of folic acid may reverse the hematological manifestations of B12 deficiency, including pernicious anemia, while not addressing the neurological manifestations). L-methylfolate may be less likely than folic acid to mask vitamin B12 deficiency.22,23 Folate therapy alone is inadequate for the treatment of a B12 deficiency.

Patient Information: Gofolate Plus® is a medical food24 to be used only under medical supervision.

4.5 Interaction with other medicinal products and other forms of interaction

**Gofolate Plus® added to other Drugs:** High dose folic acid may result in decreased serum levels for pyrimethamine and first generation anticonvulsants (carbamazepine, fosphenytoin, phenytoin, phenobarbital, primidone, valproic acid, valproate).25,26 This may possibly reduce first generation anticonvulsants effectiveness and/or increase the frequency of seizures in susceptible patients.25,26 While the concurrent use of folic acid and first generation anticonvulsants or pyrimethamine may result in decreased efficacy of anticonvulsants, no such decreased effectiveness has been reported with the use of L-methylfolate. Nevertheless, caution should be used when prescribing Gofolate Plus® among patients who are receiving treatment with first generation anticonvulsants or pyrimethamine. Pyridoxal 5’-phosphate should not be given to patients receiving the drug levodopa, because the action of levodopa is antagonized by pyridoxal 5’-phosphate. However, pyridoxal 5’-phosphate may be used concurrently in patients receiving a preparation containing both carbidopa and levodopa. Capecitabine (Xeloda®) toxicity may increase with the addition of leucovorin (5-formyltetrahydrofolate) (folate).

**Drugs added to Gofolate Plus®:** Antibiotics may alter the intestinal microflora and may decrease the absorption of methylcobalamin. Cholestyramine, colchicines or
colestipol may decrease the enterohepatic re-absorption of methylcobalamin. Metformin, para-aminosalicylic acid and potassium chloride may decrease the absorption of methylcobalamin. Nitrous oxide can produce a functional methylcobalamin deficiency. Several drugs are associated with lowering serum folate levels or reducing the amount of active folate available. First generation anticonvulsants (carbamazepine, fosphenytoin, phenytoin, phenobarbital, primidone, valproic acid, valproate)\(^{25,26}\) and lamotrigine\(^{27}\) (a second-generation anticonvulsant) may decrease folate plasma levels. Information on other second-generation anticonvulsants impact on folate levels is limited and cannot be ruled out. Diavalproex sodium,\(^{28}\) topiramate,\(^{29}\) gabapentin,\(^{30}\) pregabalin,\(^{31}\) levetiracetam,\(^{32}\) tiagabine,\(^{33}\) zonisamide,\(^{34}\) have not reported the potential to lower folate in their respective prescribing information. Methotrexate, alcohol (in excess), sulfasalazine, cholestyramine, colchicine, colestipol, L-dopa, methylprednisone, NSAIDs (high dose), pancreatic enzymes (pancrelipase, pancratin), pentamidine, pyrimethamine, smoking, triamterene, and trimethoprim may decrease folate plasma levels. Warfarin can produce significant impairment in folate status after a 6-month therapy.

### 4.6 Pregnancy and lactation

**L-methylfolate**

**Pregnancy**

- L-methylfolate has not been formally assigned a pregnancy risk category; there are no controlled studies in humans or animals
- At recommended doses, folic acid is pregnancy risk category A [adequate, wellcontrolled studies in pregnant women have failed to demonstrate risk to the fetus]
- At high doses, folic acid is pregnancy risk category C [no controlled studies in humans]
- Because pregnant women are advised to take folic acid or prenatal vitamins that contain folic acid, it is important to ask the patient about any supplements or vitamins she may be taking and consider this when deciding whether to prescribe L-methylfolate
**Breast Feeding**

- Some drug is found in mother’s breast milk

**Methylcobalamin**

- The usual precautions should be observed when administering drugs during pregnancy, especially in the first trimester
- However animal studies are insufficient with respect to effects on pregnancy/and-or/embryonal/foetal development/and-or/parturition/and-or/postnatal development. The potential risk for humans is unknown

Pyridoxal-5-phosphate is the active form of Pyridoxine

**Pyridoxine**

Pregnancy and lactation

- Data on exposed pregnancies indicate no adverse effects of pyridoxine in therapeutic doses on pregnancy or the health of the foetus or newborn child, or during lactation.
- Animal studies are insufficient with respect to effects on pregnancy, embryonal/foetal development, parturition or postnatal development.
- Caution should be exercised when prescribing to pregnant women.

There is no information available on pregnancy and lactation with the use of Gofolate plus®

**4.7 Effects on ability to drive and use machines**

No data is available regarding the effects on ability to drive and use machines.

**4.8 Undesirable effects**

While allergic sensitization has been reported following both oral and parenteral administration of folic acid, allergic sensitization has not been reported with the use of L-methylfolate. Paresthesia, somnolence, nausea and headaches have been reported with pyridoxal 5'-phosphate. Mild transient diarrhea, polycythemia vera, itching, transitory exanthema and the feeling of swelling of the entire body has been associated with methylcobalamin.
4.9 Overdose
There is no information available regarding pregnancy and lactation with the use of Gofolate plus.

5. Pharmacological properties
5.1 Pharmacodynamic properties

*L-methylfolate* or 6(S)-5-methyltetrahydrofolate [6(S)-5-MTHF], is the primary biologically active diastereoisomer of folate and the primary form of folate in circulation. It is also the form which is transported across membranes into peripheral tissues, particularly across the blood brain barrier. In the cell, 6(S)-5-MTHF is used in the methylation of homocysteine to form methionine and tetrahydrofolate (THF). THF is the immediate acceptor of one carbon units for the synthesis of thymidine-DNA, purines (RNA and DNA) and methionine. About 70% of food folate and cellular folate is comprised of 6(S)-5-MTHF. Folic acid, the synthetic form of folate, must undergo enzymatic reduction by methylenetetrahydrofolate reductase (MTHFR) to become biologically active. Genetic mutations of MTHFR result in a cell's inability to convert folic acid to 6(S)-5-MTHF.

L-methylfolate calcium is a substantially diastereoisomerically pure source of L-methylfolate containing not more than 1% D-methylfolate which results in not more than 0.03 milligrams of D-methylfolate in Gofolate Plus. D-methylfolate or 6(R)-5-methyltetrahydrofolate [6(R)-5-MTHF] is the other diastereoisomer of folate. Studies administering doses of 2.5 mg per day or higher resulted in plasma protein binding of D-methylfolate higher than L-methylfolate causing a significantly higher renal clearance of L-methylfolate when compared to D-methylfolate. Further, D-methylfolate is found to be stored in tissues in the body, mainly in the liver. D-methylfolate is not metabolized by the body and has been hypothesized to inhibit regulatory enzymes related to folate and homocysteine metabolism and reduces the bioavailability of L-methylfolate.

*Pyridoxal-5'-phosphate (PLP)* is the active form of vitamin B6 and is used as the prosthetic group for many of the enzymes where this vitamin is involved. PLP is readily absorbed by the intestine by a process which is preceded by dephosphorylation to form pyridoxal. The phosphate group is regained during passage through the intestine. Pyridoxine, the parent compound of PLP and the most frequently used form of vitamin B6, requires reduction and phosphorylation
before becoming biologically active. The PLP in Gofolate Plus® contains 25mg of pyridoxal (the active component of PLP).

*Methylcobalamin (Methyl-B12)* is one of the two forms of biologically active vitamin B12. Methyl-B12 is the principal form of circulating vitamin B12, hence the form which is transported into peripheral tissue. Methyl-B12 is absorbed by the intestine by a specific mechanism which uses the intrinsic factor and by a diffusion process in which approximately 1% of the ingested dose is absorbed. Cyanocobalamin and hydroxycobalamin are forms of the vitamin that require conversion to methylcobalamin.

5.2 Pharmacokinetic properties

*Absorption and Elimination:* L-methylfolate is a water soluble molecule which is primarily excreted via the kidneys. In a study of subjects with coronary artery disease (n=21), peak plasma levels were reached in 1-3 hours following oral/parenteral administration. Peak concentrations of L-methylfolate were found to be more than seven times higher than folic acid (129 ng/ml vs. 14.1 ng/ml) following oral/parenteral administration. The mean elimination half-life is approximately 3 hours for L-methylfolate after the administration of 5mg of oral D,Lmethylfolate. The mean values for Cmax, Tmax, and AUC were 129 ng/ml, 1.3 hr., and 383 respectively.

*Distribution:* Red blood cells (RBCs) appear to be the storage depot for folate, as RBC levels remain elevated for periods in excess of 40 days following discontinuation of supplementation. Plasma protein binding studies showed that L-methylfolate is 56% bound to plasma proteins.

5.3 Preclinical safety data

No data on animal studies of safety pharmacology, repeated-dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction and development is available.

6. Pharmaceutical particulars

6.1 List of excipients

Yellow Oxide of Iron and Titanium dioxide IP
6.2 Incompatibilities
None known

6.3 Shelf life
18 months

6.4 Special precautions for storage
Store in a dry & dark place, at a temperature not exceeding 30°C

Administrative data

7. Marketing authorisation holder
Strides Shasun Limited
Strides House, Bilekahalli,
Bannerghatta Road,
Bengaluru – 560 076, India

8. Toll free number for reporting
1800 4190601

9. Date of text
16th May 2016

10. References
24. United States Food and Drug Administration Title 21 Code of federal Regulations 101.9(j)(8).
26. Lamictal® (lamotrigine) Prescribing Information:December 2003; Mayne Pharma (USA) Inc.
27. Depakote® (divalproex sodium) Prescribing Information:January 2006; Abbott Laboratories.
28. Topamax® (topiramate) Prescribing Information:June 2005; ORTHO-McNEIL NEUROLOGICS, INC.
32. Zonegran® (zonisamide) Prescribing Information: December 2004; Eli Lilly and Company; licensed to Eisai Inc.