Package Insert
Raricap-M®

Product Summary

1. Name of the medicinal product
Raricap-M®

2. Qualitative and quantitative composition
Each Film Coated Tablet Contains
Ferrous Calcium Citrate equivalent to Iron 50 mg
Folic Acid IP 1 mg
Zinc (as Zinc Sulphate Monohydrate IP) 12.5 mg
Methylcobalamin 15 mcg
Manganese (as Manganese Sulfate Monohydrate BP) 0.2 mg
Copper (as copper Sulfate BP) 0.2 mg
Selenium (as Sodium Selenite Pentahydrate BP) 60 mcg
Pyridoxine Hydrochloride IP 1.5 mg

3. Pharmaceutical form
Film coated tablets

4. Clinical particulars
4.1 Therapeutic indications
Iron Deficiency, Iron Deficiency anaemia, megaloblastic anaemia, certain neuropathies and mineral deficiencies

4.2 Posology and method of administration
As directed by the physician

4.3 Contraindications
Known hypersensitivity to any of the active constituents
Contra-indications of Iron (Ferrous calcium citrate)

1. Haemolytic anaemia unless iron deficiency anaemia is also present
2. Haemochromatosis
3. Haemosiderosis
4. Peptic ulcer
5. Regional enteritis
6. Ulcerative colitis
7. Those receiving repeated blood transfusions

4.4 Special warnings and precautions for use

Special Precautions while taking Iron (Ferrous calcium citrate)

1. Prolonged use
2. Minimise gastrointestinal discomfort by taking along with food and gradually increasing the recommended dosage
3. Discontinue if intolerance occurs

Special Precautions while taking Folic Acid

1. In patients with undiagnosed anaemia; because it may mask pernicious anaemia
2. In pernicious anaemia and other megaloblastic anaemia where vitamin B12 is deficient

4.5 Interaction with other medicinal products and other forms of interaction

Interactions with Raricap M® are unknown. However, the known interactions for individual components are as follows

Iron component of Ferrous calcium citrate.

Iron is known to interact with other drugs like Ciprofloxacin, Clodronate, Deferiprone, Demeclocycline, Etidronic acid, Gemifloxacin, Ibandronate, Levofloxacin, Methyldopa, Moxifloxacin, Norfloxacin. Always consult your physician for the change of dose regimen or an alternative drug of choice that may strictly be required.

Pyridoxine hydrochloride

Many drugs may alter the metabolism or bioavailability of pyridoxine, including isoniazid, penicillamine and oral contraceptives, which may increase the requirements...
for pyridoxine. Pyridoxine hydrochloride may reduce the effect of levodopa, a drug used in the treatment of Parkinson’s Disease unless a dopa decarboxylase inhibitor is also given.

**Folic acid**

Folic acid is known to interact with other drugs like Fluorouracil, Sulphonamide, Phenytoin, Methotrexate, Sulfasalazine, Cholestyramine, And Zinc may affect the efficacy of Folic acid or vice versa. Always consult your physician for the change of dose regimen or an alternative drug of choice that may strictly be required.

**4.6 Pregnancy and lactation**

Iron and folic acid may be used in pregnancy. However, there is no data on any adverse events related to the use of Raricap-M®

**Methycobalamin**

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 (see section 5.3). The potential risk for humans is unknown (see section 4.8).

**Pyridoxine hydrochloride**

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.

**Folic acid**

**Pregnancy**

Folic acid deficiency during pregnancy may lead to the appearance of foetal malformations. Imbalance in folate requiring trophoblast cells may also lead to detachment of the placenta.

Very high doses of folic acid have been shown to cause foetal abnormalities in rats;
however, harmful effects in the human foetus, mother or the pregnancy have not been reported following ingestion of folic acid.

*Lactation*

Folic acid is excreted in breast milk.

No adverse effects have been observed in breast-fed infants whose mothers were receiving folic acid.

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

No information is available regarding the effect on ability to drive and use machines after using Raricap-M®.

### 4.8 Undesirable effects

Raricap-M® is well tolerated and the adverse effects are uncommon. Rarely gastrointestinal symptoms may be reported.

**Side Effects of Iron (Ferrous calcium citrate)**

1. Nausea
2. Epigastric distress
3. Vomiting
4. Constipation
5. Diarrhoea
6. Black stools
7. Temporary staining of teeth with liquid formulations.

**Pyridoxine hydrochloride**

Long term administration of large doses of pyridoxine is associated with the development of severe peripheral neuritis.

**Folic acid**

Folic acid is generally well tolerated although the following side effects have been reported:

The common side effects are

1. Urge to vomit
2. Bloating of stomach
3. Flatulence
4. Breathing difficulty
5. Loss of appetite
6. Worsening of vitamin B12 deficiency (when folic acid is used alone to treat anemia without investigating the cause).

Consult your doctor immediately if rash, itching, or breathlessness develops.

4.9 Overdose
No information on overdose with Raricap-M® is available.

Effects of Overdose of Iron (Ferrous calcium citrate)
The symptoms of overdose of iron includes vomiting diarrhea and abdominal pain in the initial stages, affecting nervous system, respiratory system, circulation and the skin, progressing towards liver failure in the later stages.

Respiratory system
• pleural effusion
• breathlessness

Nervous system
• dizziness
• convulsions
• headache
• coma

Circulation
• dehydration
• hypotension
• clotting abnormalities and bleeding
• shock

Skin
• cyanosed lips
• flushing
• pallor

Treatment includes hospitalization, immediate support of airway, respiration, and circulation. In conscious patients induce emesis with ipecac; if not empty stomach by
gastric lavage. Follow emesis with lavage, using a 1% sodium bicarbonate solution to convert iron to less irritating poorly absorbed form. Take abdominal X-ray to determine presence of excess iron. Deferoxamine may be used for systemic chelation as required.

**Effects of Overdose of Folic Acid**
Relatively non toxic. Provide symptomatic treatment and supportive measures.

**Effects of overdose of methycobalamin**
Relatively non toxic

### 5. Pharmacological properties

#### 5.1 Pharmacodynamic properties

**Mechanism of Action of Iron (Ferrous calcium citrate)**
- Ferrous calcium citrate exerts haematinic action by being an essential constituent of haemoglobin. It is necessary for the oxidative process of living tissues.

**Mechanism of Action of Folic Acid**
Folic acid reduced by enzymes folate reductase and dihydrofolate reductase and forms dihydrofolic acid tetrahydrofolic acid respectively. Tetrahydrofolic acid acts as a coenzyme which mediates a number of one carbon transfer reactions by carrying a methyl group as an adduct. It involves a number of reactions such as
  1. Conversion of homocysteine to methionine.
  2. Synthesis of thymidylate which is an essential constituent of DNA from methylene-tetrahydrofolic acid.
  3. Conversion of serine to glycine by tetrahydrofolic acid and forms methylene-tetrahydrofolic acid.
  4. To introduce carbon units at position 2 and 8 during de novo purine synthesis requires formyl-tetrahydrofolic acid and methenyl-tetrahydrofolic acid.
  5. Generation and utilization of "formate pool".
  6. For mediating formino group transfer in histidine metabolism. Folic acid is required to maintain normal erythropoiesis and nucleoprotein synthesis.
Methycobalamin

- It is a Neurotropic and acts as a growth promoter for nerve cells, a property which helps to regenerate Central and Peripheral nervous tissue damaged in disorder such as diabetic peripheral neuropathy.
- It acts as a methyl donor for the synthesis of Lecithin, a major component of the Myelin sheath. This enzyme is involved in the conversion of the amino acid homocysteine into methionine which is, in turn, required for DNA methylation. The other form, 5-deoxyadenosylcobalamin, is a cofactor needed by the enzyme that converts L-methylmalonyl-CoA to succinyl-CoA. This conversion is an important step in the extraction of energy from proteins and fats. Furthermore, succinyl CoA is necessary for the production of hemoglobin, the substance that carries oxygen in red blood cells.
- In the absence of coenzyme B12, tetrahydrofolate cannot be regenerated from its inactive storage form, 5-methyl tetrahydrofolate, resulting in functional folate deficiency
- It acts as a co-factor in the enzyme methionine synthase which regenerates methionine thus generating an increased supply of S-Adenosyl Methionine (SAMe) and SAMe protects from Neurotoxicity.
- It improves the excitability of the nerve fibres and thus improves the neurotransmission.

Pyridoxine hydrochloride

Pyridoxine hydrochloride is Vitamin B6. It is converted to pyridoxal phosphate which is the co-enzyme for a variety of metabolic transformations. It is essential for human nutrition.

5.2 Pharmacokinetic properties

Pharmacokinetics of Iron (Ferrous calcium citrate)

Absorption: Absorbed orally in ferrous form and poorly absorbed in healthy individuals (about 10%) but in patients suffering from iron deficiency anaemia up to 60% dose is absorbed.

Distribution: Transported in a transferrin bound form into bone marrow for incorporation into haemoglobin.
Metabolism: Iron liberated by destruction of haemoglobin is reused by the body.

Excretion: Excretion of iron is minimal. Loss usually occurs in nails, faeces, urine, hair, sweat, and bile.

Pharmacokinetics of Folic Acid
Absorption: Well absorbed orally
Distribution: Widely distributed in the body and highest concentration is seen in liver.
It appears in the CSF and breast milk
Metabolism: Metabolized in to N-methyl tetrahydrofolic acid in liver
Excretion: Extra drug is excreted unchanged in urine. A small portion of folate is lost by a combination of urinary and fecal excretion and oxidative cleavage of molecule.

Pharmacokinetics of Pyridoxine hydrochloride
Pyridoxine hydrochloride is absorbed from the gastrointestinal tract and is converted to the active forms pyridoxal phosphate and pyridoxamine phosphate. It crosses the placental barrier and appears in breast milk. It is excreted in the urine as 4-pyridoxic acid.

5.3 Preclinical safety data
No data is available on preclinical safety with Raricap-M®.

For Folic acid separately
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.

6. Pharmaceutical particulars

6.1 List of excipients
Excipients q.s
Overages are added to compensate active degradation during shelf life.
6.2 Incompatibilities
None known.

6.3 Shelf life
24 Months.

6.4 Special precautions for storage
Store in the original package below 30°C protected from light, keep all medicine out of reach of children.

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
5th July 2016