1.0 Name of the medicinal product

EMZOVIT INSTANT MICRONUTRIENT POWDER

2.0 Qualitative and quantitative composition

VITAMIN A 400µG,

VITAMIN D3 5.00µG,

VITAMINE E 5.00MG,

VITAMIN B1 0.50MG,

VITAMIN B2 0.50MG

3.0 Pharmaceutical form

Powder for solution

4. Clinical particulars

4.1 Therapeutic indications

Fortify food with vital nutrients for children

4.2 Posology and method of administration

Emzovit Instant Micronutrient Powder may be included in the composition of nutritive mixtures combining carbohydrates, lipids, amino acids and electrolytes provided that compatibility and stability have been confirmed for each nutritive mixture, to meet nutrient needs and prevent deficiencies and complications from developing.

The total vitamin amounts from all sources such as nutritional sources, other vitamin supplements, or medications that contain vitamins as inactive ingredients should be considered.

The patient's clinical status and vitamin levels should be monitored to ensure maintenance of adequate levels.

It should be taken into account that some vitamins, especially A, B2, and B6 are sensitive to ultraviolet light (e.g., direct or indirect sun light). In addition, loss of vitamins A, B1, C, and E may increase with higher levels of oxygen in the solution. These factors should be considered if adequate vitamin levels are not achieved.

4.3 Contraindications

Emzovit Instant Micronutrient Powder must not be used in:

- hypersensitivity to the active substances, especially vitamin B1 or to any of the excipients including soy protein/products (lecithin in mixed micelle is soy-derived) or peanut protein/products,

- hypervitaminosis from any vitamin contained in this formulation,

4.4 Special warnings and precautions for use

WARNINGS

Hypersensitivity Reactions

• Severe systemic hypersensitivity reactions have been reported with Emzovit other multivitamin preparations, and individual vitamins (including B1, B2, B12 and folic acid). Reactions with fatal outcome have been reported with Emzovit and other parenteral vitamin products

• Cross-allergic reactions between soybean and peanut proteins have been observed.

• In some cases, the manifestations of a hypersensitivity reaction during intravenous administration of multivitamins may be rate related. If infused intravenously, Emzovit should be administered slowly. If injected intravenously, the injection must be administered slowly (over at least 10 minutes).

• The infusion or injection must be stopped immediately if signs or symptoms of a hypersensitivity reaction develop.

Vitamin Toxicity

• The patient's clinical status and blood vitamin concentrations should be monitored to avoid overdose and toxic effects, especially with vitamins A, D and E, and in particular in patients who receive additional vitamins from other sources or use other agents that increase the risk of vitamin toxicity.

• Monitoring is particularly important in patients receiving long-term supplementation.

Hypervitaminosis A

• The risk for hypervitaminosis A and vitamin A toxicity (e.g., skin and bone abnormalities, diplopia, cirrhosis) is increased in, for example:

-patients with protein malnutrition,

-patients with renal impairment (even in the absence of vitamin A supplementation),

-patients with hepatic impairment,

-patients with small body size (e.g., paediatric patients), and

-patients on chronic therapy.

• Acute hepatic disease in patients with saturated hepatic vitamin A stores can lead to the manifestation of vitamin A toxicity.

Refeeding Syndrome in Patients Receiving Parenteral Nutrition

Refeeding severely undernourished patients may result in refeeding syndrome that is characterized by the shift of potassium, phosphorus, and magnesium intracellularly as the patient becomes anabolic. Thiamine deficiency and fluid retention may also develop. Careful monitoring and slowly increasing nutrient intakes while avoiding overfeeding can prevent these complications. Should nutrient deficiencies occur, appropriate supplementation may be warranted.

Precipitates in Patients Receiving Parenteral Nutrition

Pulmonary vascular precipitates have been reported in patients receiving parenteral nutrition. In some cases, fatal outcomes have occurred. Excessive addition of calcium and phosphate increases the risk of the formation of calcium phosphate precipitates. Precipitates have been reported even in the absence of phosphate salt in the solution. Precipitation distal to the in-line filter and suspected precipitate formation in the blood stream have also been reported.

In addition to inspection of the solution, the infusion set and catheter should also periodically be checked for precipitates.

If signs of pulmonary distress occur, the infusion should be stopped and medical evaluation initiated.

PRECAUTIONS

Hepatic Effects

• Monitoring of liver function parameters is recommended in patients receiving Emzovit Particularly close monitoring is recommended in patients with hepatic jaundice or other evidence of cholestasis.

In patients receiving Emzovit, instances of liver enzyme increases have been reported, including isolated alanine aminotransferase (ALT) increases in patients with inflammatory bowel disease (see section 4.8).

In addition, an increase in bile acid levels (total and individual bile acids including glycocholic acid) have been reported in patients receiving Emzovit.

• Hepatobiliary disorders including cholestasis, hepatic steatosis, fibrosis and cirrhosis, possibly leading to hepatic failure, as well as cholecystitis and cholelithiasis are known to develop in some patients on parenteral nutrition (including vitamin supplemented parenteral nutrition). The etiology of these disorders is thought to be multifactorial and may differ between patients. Patients developing abnormal laboratory parameters or other signs of hepatobiliary disorders should be assessed early by a clinician knowledgeable in liver diseases in order to identify possible causative and contributory factors, and possible therapeutic and prophylactic interventions.

Use in Patients with Impaired Hepatic Function

Patients with hepatic impairment may need individualized vitamin supplementation. Particular attention should be placed on preventing vitamin A toxicity, because the presence

of liver disease is associated with increased susceptibility to vitamin A toxicity, in particular in combination with chronic excessive alcohol consumption

Use in Patients with Impaired Renal Function

Patients with renal impairment may need individualized vitamin supplementation, depending on the degree of renal impairment and the presence of concomitant medical conditions. In patients with severe renal impairment, particular attention should be placed on maintaining adequate vitamin D status and preventing vitamin A toxicity, which may develop in such patients with low-dose vitamin A supplementation or even without supplementation.

Pyridoxine (vitamin B6) hypervitaminosis and toxicity (peripheral neuropathy, involuntary movements) have been reported in patients on chronic haemodialysis receiving intravenous multivitamins containing 4 mg pyridoxine administered three times a week.

General Monitoring

Clinical status and vitamin levels should be monitored in patients receiving parenteral multivitamins as the only source of vitamins for extended periods of time. It is particularly important to monitor for adequate supplementation of, for example:

• Vitamin A in patients with pressure ulcers, wounds, burns, short bowel syndrome or cystic fibrosis

• Vitamin B1 in dialysis patients

• Vitamin B2 in cancer patients

• Vitamin B6 in patients with renal impairment

• Individual vitamins whose requirements may be increased due to interactions with other medicines

Deficiency of one or more vitamins must be corrected by specific supplementation.

Vitamin K

Emzovit does not contain Vitamin K. Vitamin K must be administered separately if necessary.

Use in Patients with Vitamin B12 Deficiency

Evaluation of vitamin B12 status is recommended before starting supplementation with Emzovit in patients at risk for vitamin B12 deficiency and/or when supplementation with Emzovit over several weeks is planned.

After several days of administration, both the individual amounts of cyanocobalamin (vitamin B12) and folic acid in Emzovit may be sufficient to result in an increase in red blood cell count, reticulocyte count, and haemoglobin values in some patients with vitamin B12 deficiency-associated megaloblastic anaemia. This may be masking an existing vitamin B12 deficiency. Effective treatment of vitamin B12 deficiency requires higher doses of cyanocobalamin than provided in Emzovit.

Folic acid supplementation in patients with vitamin B12 deficiency, who do not also receive vitamin B12, does not prevent the development or progression of neurologic manifestations associated with the vitamin B12 deficiency. It has been suggested that neurologic deterioration may even be accelerated.

When interpreting levels of vitamin B12, it should be taken into account that recent intake of vitamin B12 may result in normal levels despite a tissue deficiency.

4.5 Interaction with other medicinal products and other forms of interaction

Interactions between specific vitamins in Emzovit and other agents should be managed accordingly.

Such interactions include:

• Agents that can cause pseudotumor cerebri (including certain tetracyclines): Increased risk for pseudotumor cerebri by concomitant administration of Vitamin A

• Alcohol (chronic excessive consumption): Increases the risk of vitamin A hepatotoxicity

• Anticonvulsants (phenytoin, fosphenytoin, phenobarbital, primidone): Folic acid supplementation can decrease the anticonvulsant serum concentration and increase seizure risk.

• Antiplatelet agents (e.g., aspirin): Vitamin E can add to the inhibition of platelet function

• Aspirin (high dose therapy): Can reduce folic acid levels by increasing urinary excretion

• Certain anticonvulsants (e.g., phenytoin, carbamazepine, phenobarbital, valproate): Can cause folate, pyridoxine and vitamin D deficiencies

• Certain antiretroviral agents: Decreased vitamin D levels have been associated with, e.g., efavirenz and zidovudine. Decreased formation of the active vitamin D metabolite has been associated with protease inhibitors.

• Chloramphenicol: Can inhibit the haematological response to vitamin B12 therapy

• Deferoxamine: Increased risk of iron-induced cardiac failure due to increased iron mobilization by supraphysiologic vitamin C supplementation. For specific precautions, refer to deferoxamine product information.

• Ethionamide: Can cause pyridoxine deficiency

• Fluoropyrimidines (5-fluorouracil, capecitabine, tegafur): Increased cytotoxicity when combined with folic acid

• Folate antagonists, e.g., methotrexate, sulfasalazine, pyrimethamine, triamterene, trimethoprim, and high doses of tea catechins: Block the conversion of folate to its active metabolites and reduce the effectiveness of supplementation

• Folate antimetabolites (methotrexate, raltitrexed): Folic acid supplementation can decrease the antimetabolite effects

• Levodopa: The content of pyridoxine may interfere with the effects of concurrent levodopa therapy.

• Pyridoxine antagonists, including cycloserine, hydralazine, isoniazid, penicillamine, phenelzine: Can cause pyridoxine deficiency

• Retinoids, including bexarotene: Increase the risk of toxicity when used concomitantly with vitamin A

• Theophylline: Can cause pyridoxine deficiency

• Tipranavir oral solution: Contains 116 IU/mL of vitamin E, which is in excess of the daily recommended intake

• Vitamin K antagonists (e.g., warfarin): Enhanced anticoagulant effect by vitamin E

4.6 Fertility, pregnancy and lactation

Physicians should carefully consider the potential risks and benefits for each specific patient before prescribing Emzovit

Pregnancy

No safety data are available for Emzovit administered during pregnancy or in breastfeeding women. This medicinal product may be prescribed during pregnancy if required, providing the indication and dosages are observed in order to avoid vitamin overdose.

Lactation

Use is not recommended during breastfeeding because of the risk of vitamin A overdose in the neonate.

Fertility

There are no adequate data from the use of Emzovit with regards to fertility in male or female patients.

4.7 Effects on ability to drive and use machines

There is no information on the effects of Emzovit on the ability to operate an automobile or other heavy machinery.

4.8 Undesirable effects

- ✓ respiratory distress,
- ✓ chest discomfort,
- ✓ throat tightness,
- ✓ urticaria,
- ✓ rash,
- ✓ erythema,

- ✓ epigastric discomfort,
- ✓ Nausea
- ✓ Vomiting
- ✓ Diarrhoea
- ✓ Pruritus

4.9 Overdose

Acute or chronic overdose of vitamins (in particular A, B6, D, and E) can cause symptomatic hypervitaminosis.

The risk of overdose is particularly high if a patient receives vitamins from multiple sources and overall supplementation of a vitamin does not match the patient's individual requirements, and in patients with increased susceptibility to hypervitaminosis

Treatment of vitamin overdose usually consists of withdrawal of the vitamin and other measures as clinically indicated.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Balanced association of all water soluble and fat soluble, vitamins essential for metabolism, with the exception of Vitamin K.

5.2 Pharmacokinetic properties

Not applicable.

5.3 Preclinical safety data

Not applicable.

6. Pharmaceutical particulars

6.1 Incompatibilities

Vitamin A and thiamine in Emzovit may react with bisulfites in parenteral nutrition solutions (e.g., as a result of admixtures) leading to degradation of vitamin A and thiamine.

Folic acid stability can be impaired with increased calcium concentrations in an admixture.

6.2 Shelf life

Unopened: 2 years

6.3 PACK SIZE: SACHET, 1G X 30

6.4 Marketing Authorisation Number: A11-0320

Manufactured by

Emzor Pharmaceutical Industries Limited

Km 1 Flowergate Mixed Development Scheme,

Sagamu/Benin Expressway,Makun, Sagamu,Ogun-State.