Summary of Product Characteristics for Pharmaceutical Products

1. Name of the medicinal product:

Multibionta Injection

2. Qualitative and quantitative composition:

Each 10 ml Ampoule contains:
Vitamin A (Palmitate)..... 10,000I.U
Vitamin B1(Thiamine Mononitrate),.....50mg
Riboflavin-5-Phosphate Sodium.....10mg
Vitamin B6(Pyridoxine Hydrochloride).....15mg
Nicotinamide.....100mg
Dexpanthenol.....25mg
Vitamin C (Ascorbic Acid).....500mg
Vitamin E (dl- Alpha Tocopheryl Acetate).....5mg

For a full list of excipients, see section 6.1.

3. Pharmaceutical form

Solution for I.V. Infusion
Yellowish Orange Fluorescence Solution

4. Clinical particulars

4.1 Therapeutic indications

Multibionta Injection for Infusion has extremely wide field of indications.
To promote the recovery after severe illness, severe vomiting, post-operative restrictions of oral nutrition's, in burns and many other conditions where parenteral nutrition is required.
In the treatment of complex vitamin deficiencies.
To augment glucose therapy.
To improve mental functions.
To prevent and control the side effects of sulphonamide antibiotics and tuberculosis.

4.2 Posology and method of administration

Dosage

Adults and children aged over 11 years : 1 vial/day.

DOSAGE AND ADMINISTRATION
One 10 ml ampoule daily by infusion or as prescribed by the physician.
Immediately before use, the contents of the ampoule must be added to

a full infusion bottle containing not less than 250 ml of infusion solution. To avoid frothing, the mixture should be inverted gently. It should not be shaken. A mixture should be discarded if visible turbidity or crystallization appears in the infusion solution. In order to minimize possible loss of active substance in a mixture (masked incompatibility), it is recommended that solution to which this product is added should be used within 8 hours.
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

Multibionta Injection is contraindicated in patients known to be hypersensitive to any of its components. Hypervitaminosis from any vitamin contained in this formulation

4.4 Special warnings and precautions for use

Caution should be exercised when dosing ascorbic acid in patients with chronic renal failure and in patients receiving acetylsalicylic acid.

Allergic Reactions to Thiamine

Allergic reactions such as urticaria, periorbital and digital edema, have been reported following intravenous administration of thiamine. There have been rare reports of anaphylaxis following intravenous doses of thiamine. No fatal anaphylaxis reactions have been reported.

Hypersensitivity Reactions

Severe systemic hypersensitivity reactions have been reported with multibionta other multivitamin preparations, and individual vitamins (including B1, B2, B12 and folic acid). Reactions with fatal outcome have been reported with multibionta and other parenteral vitamin products (See Section 4.8).

In some cases, the manifestations of a hypersensitivity reaction during intravenous administration of multivitamins may be rate related. If infused intravenously, multibionta 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.

Potential to Develop Vitamin Deficiencies or Excesses

In patients receiving parenteral multivitamins, blood vitamin concentrations should be periodically monitored to determine if vitamin deficiencies or excesses are developing.

Interference with Urine Glucose Testing

Vitamin C which is also known as ascorbic acid, in the urine may cause false negative urine glucose determinations.

ADVERSE EFFECTS

Allergic reactions, including rash, pruritus, erythema and anaphylaxis have been reported with Vitamin use. Components of this product have been associated with gastrointestinal effects such as heartburn, eructation, abdominal pain and cramps, diarrhea, vomiting, nausea, and anorexia. Hepatic dysfunction with abnormal liver function tests, including hyperbilirubinemia has been noted. Deterioration of acneiform vulgaris, or eruption of acneiform exanthema, has been noted with several components. Bright yellow urine discoloration has been reported with riboflavin usage. Niacinamide has strong vasodilator effects, most often characterized by flushing, dizziness, or faintness. Peripheral sensory neuropathies have been noted with the use of pyridoxine. With ascorbic acid usage, stone formation, crystalluria, and oxalosis have been reported in the literature.

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 (See also Hypervitaminosis A and Hepatic Effects above

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 (see section 4.5).

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

Use in Patients with Vitamin B12 Deficiency

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

After several days of administration, both the individual amounts of cyanocobalamin (vitamin B12) and folic acid in Multibiontin 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 Multibiontin

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

With concomitant use of niacinamide and alcohol, toxic delirium and lactic acidosis have been noted. Concomitant use of niacinamide and nicotine has been reported to cause increased flushing and dizziness. Since pyridoxine is noted to have effects on dopamine, drug interactions are possible. A drug interaction with Levodopa is noted but can be avoided if Levodopa is given in combination with a decarboxylase inhibitor. Serum phenytoin and phenobarbital levels have been reported to decrease in patients receiving 80 to 200 mg/day of pyridoxine. Use of anticonvulsants and sulfasalazine has been associated with folate deficiency, even when folic acid is supplied orally. Prothrombin times are decreased when ascorbic acid is used concomitantly with anticoagulants. Thiamine, riboflavin, pyridoxine, niacinamide, and ascorbic acid decrease antibiotic activities of erythromycin, kanamycin, streptomycin, doxycycline, and lincomycin. Ascorbic acid and riboflavin inactivate bleomycin in vitro, thus the activity of bleomycin may be reduced. Concomitant administration of hydralazine or isoniazid may increase pyridoxine requirements.
Iinteractions between specific vitamins in Cernevit 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 (see section 4.4: Hypervitaminosis 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

Drugs that Bind to alpha1-Acid Glycoprotein (AAG):

In an in vitro study using human serum, concentrations of glycocholic acid approximately 4 times higher than the glycocholic acid serum concentration that would result from a bolus injection of Multbionta in adults, increased the unbound fraction of selected drugs known to bind to alpha1-acid glycoprotein (AAG) by 50-80%.
It is not known whether this effect is clinically relevant if the amount of glycocholic acid contained in a standard multbionta dose (as a component of the mixed micelles) is administered by slow intravenous injection, intramuscular injection, or infused over a longer period of time.
Patients receiving Multibionta as well as drugs that bind to AAG should be closely monitored for increases in response of these drugs. These include propranolol, prazosin, and numerous others.

<u>Interactions with Additional Vitamin Supplementation:</u>

Some medications can interact with certain vitamins at doses markedly higher than those provided with Multibionta. This should be taken into consideration in patients receiving vitamins from multiple sources, and

when applicable, patients should be monitored for such interactions and managed accordingly.

Such interactions include:

• Amiodarone: Concomitant use of vitamin B6 can enhance amiodarone-induced photosensitivity.

• Agents with anticoagulant effects (e.g., such as abciximab, clopidogrel, heparin, warfarin): Increased bleeding risk due to additional risk of bleeding associated with high vitamin A doses

• Carbamazepine: Inhibition of metabolism associated with large nicotinamide doses

• Chemotherapeutic agents that rely on the production of reactive oxygen species for their activity: Possible inhibition of chemotherapy activity by the antioxidant effects of high doses of vitamin E

• Insulin, antidiabetic agents: Decreased insulin sensitivity associated with large nicotinamide doses

• Iron: High dose-supplementation with vitamin E may reduce the haematological response to iron in anaemic patients

• Oral contraceptives (combination hormone types): High doses of vitamin C have been associated with breakthrough bleeding and contraceptive failure

• Phenobarbital: Increased metabolism/lower serum levels and reduced effect associated with large pyridoxine doses

• Phenytoin, fosphenytoin: Lower serum levels associated with large pyridoxine doses

• Primidone: Decreased metabolism to phenobarbital and increased primidone levels associated with large nicotinamide doses

Fertility, pregnancy, and lactation

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

Pregnancy

No data on pregnancy

Lactation

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

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Fertility
No adequate data

4.6 Effects on ability to drive and use machines.

No data yet

4.7 Undesirable effects

Summary of the safety profile

Tabulated list of adverse reactions

Adverse reactions in Table 1 are listed according to MedDRA system organ class and frequency category. Frequency categories are defined using the following convention: very common (≥1/10); common (≥1/100 to<1/10, uncommon(≥1/1000 to <1/100; rare(≥1/10,000 to <1/1000, very rare (<1/10,000); not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

System Organ Class	Frequency	Preferred MedDRA Term
Nervous system disorders	Uncommon	Dysgeusia (metallic taste)
Immune system disorders	Not known**	Systemic hypersensitivity reactions with manifestations such as respiratory distress, chest discomfort, throat tightness, urticaria, rash, erythema, epigastric discomfort, as well as cardiac arrest with fatal outcome
Metabolism and nutrition disorders	Common Uncommon	Vitamin A increased[2,3], Retinol binding protein increased
Cardiac disorders	Not known	Tachycardia
Respiratory, thoracic and mediastinal disorders	Uncommon	Tachypnea
Gastrointestinal disorders	Common Uncommon Not known**	Nausea Vomiting Diarrhoea
Hepatobiliary disorders	Uncommon	Transaminases increased, Isolated alanine aminotransferase increased[4], Glutamate dehydrogenase increased, Blood alkaline phosphatase increased, Bile acids increased[5] Gamma-glutamyltransferase increased
Skin and subcutaneous tissue disorders	Uncommon	Pruritus
General disorders and administration site conditions	Uncommon *	Injection/Infusion Site Pain Pyrexia, Generalized aching, infusion site reactions, i.e., burning sensation, rash

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4.8 Overdose

Acute or chronic overdose of vitamins (in particular A, B6, 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 (see section 4.4).
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 the metabolism of the adult and the child aged over 11 years

5.2 Pharmacokinetic properties

Not applicable

5.3 Preclinical safety data

Not applicable

6. Pharmaceutical particulars

6.1 List of excipients

Glycine
Glycocholic acid
Soybean phosphatides
Sodium hydroxide
Hydrochloric acid, Concentrated

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.
• Additives may be incompatible with parenteral nutrition containing Multibionta.
• If co-administration of drugs that are incompatible at the Y-site is necessary, administer via separate IV lines.
• Vitamin A and thiamine in Multibiontina may react with bisulfites in parenteral nutrition solutions (e.g., as a result of admixtures) leading to degradation of vitamin A and thiamine.
• An increase in pH of a solution may increase the degradation of some vitamins. This should be considered when adding alkaline solutions to the admixture containing Multibiontina.

6.3 Shelf life
18 months

6.4 Special precautions for storage:

Store below 30 °C. Protect from light and heat.
Keep all the medications out of the reach of Children.

6.5 Nature and contents of container
Multibionta injection **5x10ml** stored in printed Ambered Colored Glass Ampoule and Bottle is packed in a unit carton with insert.

6.6 Special precautions for disposal and other handling:
No data

7. Marketing authorization holder and manufacturing site addresses

Marketing authorization holder:
Company) Name: Martin Dow Marker Limited
Address: 7-Jail, Road Quetta,
Country: Pakistan
Telephone: +92-81-111523523
E-Mail: info@martindowmarker.com
Manufacturing site address:
Name: Martin Dow Marker Limited
Company name: Martin Dow Marker Limited
Address:7-Jail Road, Quetta,
Country: Pakistan
Telephone: +92-81-111523523
E-Mail: info@martindowmarker.com

8. Marketing authorization number
CTD10036

9. Date of first registration
26/05/2023

10. Date of revision of the text:
September 2023

11. Dosimetry:
Not Applicable

12. Instructions for Preparation of Radiopharmaceuticals:
Not Applicable

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