Baxter

CERNEVIT
Multivitamin

Presentation

Each vial contains:

Retinol Palmitat	
Amount corresponding to retinol	3500 IU
Cholecalciferol	220 IU
DL alphatocopherol	10.200 mg
Amount corresponding to alphatocopherol	11.200 IU
Ascorbic Acid	125.000 mg
Cocarboxylase tetrahydrate	5.800 mg
Amount corresponding to Thiamine	3.510 mg
Riboflavine sodium phosphate dihydrate	5.670 mg
Amount corresponding to Riboflavine	4.140 mg
Pyridoxine Hydrochloride	5.500 mg
Amount corresponding to Pyridoxine	4.530 mg
Cyanocobalamine	0.006 mg
Folic Acid	0.414 mg
Dexpanthenol	16.150 mg
Amount corresponding to Pantothenic Acid	17.250 mg
Biotin	0.069 mg
Nicotinamide	46.000 mg
Glycine	250.000 mg
Glycocholic Acid	140.000 mg
Soya Lecithin	112.500 mg
Sodium hydroxide	q.s. pH=5.9
Hydrochloric acid	

CERNEVIT is a multivitamin preparation of both water soluble and fat soluble vitamins (except vitamin K) combined with mixed micelles (glycocholic acid and lecithin). Redresses the body's vitamin requirements which may be diminished due to various stress situations (trauma, surgery, burns, infections) which are likely to slow the healing process.

Uses

CERNEVIT is indicated when the daily requirements of vitamins are required to be given to the patient by the parenteral route because oral administration is either contraindicated, impossible or insufficient (e.g due to malnutrition, gastrointestinal malabsorbtion, etc).

Contraindications, Warning, etc.

Contraindication

CERNEVIT is contraindicated in patients with pre-existing hypervitaminosis or known hypersensitivity to any of the active constituent in particular patients with hypersensitivity to Thiamine (Vitamin B1) or soy proteins/products (lecithin in mixed micelle is soy-derived).

Special Warnings and Precautions for Use

WARNINGS

Anaphylactic reactions may occur in allergic subjects because of the presence of vitamin B1. Mild allergic reactions such as sneezing or mild asthma are warning signs that a further injection may give rise to anaphylactic shock.

Hypersensitivity Reactions

- Severe systemic hypersensitivity reactions have been reported with CERNEVIT, other multivitamin preparations, and individual vitamins (including B1, B2, B12 and folic acid). Reactions with fatal outcome have been reported with CERNEVIT and other parenteral vitamin products.
- In some cases, the manifestations of a hypersensitivity reaction during intravenous administration of multivitamins may be rate related. If infused intravenously, CERNEVIT 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.
- Cernevit contains soy-derived lecithin and should be used with caution in patients with peanut allergies due to potential cross-reactivity.

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., pediatric 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

Caution should be exercised when administering CERNEVIT to patients who may be receiving Vitamin A from other sources. Following intravenous bolus injection, a moderate rise only in SGPT transaminases has been noted in some patients with active inflammatory enterocolitis. Increased levels are rapidly reversible following the interruption of administration. It is advisable to monitor transaminase levels in patients of this type. Also in the case of impaired kidney function, lipid soluble vitamin levels should be carefully monitored. CERNEVIT does not contain Vitamin K. If this vitamin is required by the patient, it must be administered separately.

CERNEVIT should not be given as a direct, undiluted intravenous injection as it may give rise to dizziness, faintness and possible tissue irritations.

Daily vitamin requirements must be calculated to avoid overdosage and toxic effects, especially with regard to vitamins A and D in pediatric patients.

In patients for whom total parenteral nutrition will be continued for long periods of time, vitamins A,C,D and Folic acid blood levels should be monitored.

Hepatic Effects

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

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

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

- 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.

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

- CERNEVIT does not contain vitamin K, which should be administered separately if necessary.

Laboratory Test Interferences

Depending on the reagents used, the presence of ascorbic acid in blood and urine may cause false high or low glucose readings in some urine and blood glucose testing systems, including test strips and handheld glucose meters. The technical information for any laboratory test should be consulted to determine the potential interference from vitamins.

Biotin may interfere with laboratory tests that are based on a biotin/streptavidin interaction including tests used in emergency situations. The interference may result in either falsely decreased or falsely increased test results, depending on the assay. The risk of interference is higher in children and patients with renal impairment and increases with higher doses. Cases of interference with laboratory tests based on a biotin/streptavidin interaction have been reported in adults receiving high daily biotin oral doses of 5 to 300 mg.

The recommended daily dose of Cernevit contains a dose of 69 µg biotin and thus, there is minimal risk for laboratory interference when Cernevit is administered as part of a parenteral nutrition infusion over 12-24 hours. However, biotin plasma concentrations that interfere with certain assays may be reached in some patients e.g. when the daily dose is administered as a bolus injection over 10 minutes (see section 4.2), in patients of low weight, and when Cernevit is administered over 12 to 24 hours to children or to patients with renal impairment.

When interpreting results of laboratory tests, possible biotin interference must be taken into consideration, especially if lack of coherence with the clinical presentation is observed (e.g. inaccurate thyroid test results mimicking Grave´s disease in asymptomatic patients or falsely low troponin T test results in patients with myocardial infarction).

Consult laboratory personnel for alternative tests in cases where biotin interference is suspected.

Sodium Content

CERNEVIT contains 24 mg sodium (1 mmoL) per vial. This should be taken into consideration if patients are on a controlled sodium diet.

Pediatric Use

CERNEVIT is indicated in pediatric patients over 11 years of age.

Pregnancy and Lactation

The use of CERNEVIT has not been studied in human pregnancy. Experimental animal studies are insufficient to assess the safety with respect to the development of the embryo or foetus, the course of gestation, and peri and post-natal development.

It is recommended therefore that this product should not be used in pregnancy. Since vitamins are known to be excreted in breast milk, this product should also not be used in women who are breast feeding.

Interactions with Other Medicinal Products and Other Forms of Interactions

- The dosage of drugs known to be influenced by folic acid, for example phenytoin must be carefully monitored. Folic acid may obscure pernicious anaemia.
- Pyridoxine can reduce the effect of levodopa.
- It has been reported that Folic Acid is unstable in the presence of calcium salts such as calcium gluconate.
- Some of the vitamins in CERNEVIT may react with Vitamin K Bisulfite.
- Direct addition of CERNEVIT to intravenous fat emulsions is not recommended.
- Agents that can cause pseudotumor cerebri (including certain tetracyclines): Increased risk for pseudotumor cerebri (benign/idiopathic intracranial hypertension) 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 hematological 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
- 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 CERNEVIT 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 CERNEVIT 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 CERNEVIT 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.

Interactions with Additional Vitamin Supplementation:

Some medications can interact with certain vitamins at doses markedly higher than those provided with CERNEVIT. 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 hematological response to iron in anemic 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

Dosage and Administration

Adults and children over 11 years of age should receive the contents of one vial per day. 5 ml of water for injections should first be added by syringe into the vial and gently mixed to dissolve the lyophilised powder. The resultant solution should then be administered by slow intravenous injection (at least 10 minutes) or by infusion in either isotonic saline or glucose solution. CERNEVIT may be included in the composition of parenteral nutrition mixtures combining carbohydrates, lipids, amino acids, electrolytes and trace elements, provided that compatibility and stability have been confirmed. It is presented as an odourless orange-yellow lyophilised cake of sterile powder to be reconstituted with 5 ml of water for injection Ph. Eur. Or other intravenous fluids such as Sodium Chloride 5%, glucose or nutrition mixture prior to parenteral administration. When reconstituted with water for injection, the solution has a pH of approximately 5.9.

Adverse Reactions

Allergic reactions have been known to occur following intravenous administration of Thiamine and to other members of the B-complex present in the solution. There have been rare reports of anaphylactoid reactions following large intravenous doses of Thiamine. The risk, however, is negligible if Thiamine is coadministered with other B-group vitamins. There have been rare reports of the following types of reactions:

- Dermatological: Rash,erytheme,pruritus
- Central nervous System: Headache, dizziness, agitation, anxiety
- Opthalmic: Diplopia
- Allergic: Urticaria, periorbital and digital oedema

Persons susceptible to the effects of Nicotinamide may experience flushing, itching or burning of the skin after infusion.
The adverse reactions listed in Table 1 below have been identified from 3 clinical studies assessing the local and systemic tolerance of CERNEVIT in adult patients (N = 267) requiring a parenteral vitamin supplement. In all three studies, CERNEVIT was administered intramuscularly for 5 days, slow intravenous push for 5 days, and as an intravenous infusion for 10 days.

Table 1: Clinical Trials Adverse Reactions

System Organ Class (SOC)	Preferred MedDRA Term	Frequency per Patient N = 267		Frequency per Administration N = 1765	
		Category	Number of patients (Percentage)	Category	Number of occurrences (Percentage)
GASTROINTESTINAL DISORDERS	Vomiting	Uncommon	1 (0.37%)	Uncommon	3 (0.17%)
	Nausea	Uncommon	1 (0.37%)	Uncommon	3 (0.17%)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	Injection/ Infusion Site Pain	Common	20 (7.49%)	Unknown*	Unknown*

Legend: Frequency is based upon the following scale: Very Common (≥1/10); Common (≥1/100 - <1/10), Uncommon (≥1/1,000 - <1/100), Rare (≥1/10,000 - <1/1,000), Very Rare (<1/10,000)

* Injection/infusion site pain was reported after intramuscular, intravenous push, and intravenous infusion administration of CERNEVIT. The frequency per administration cannot be determined from the reported data.

The following additional adverse reactions listed in Table 2 below have been identified from other multiple clinical studies (of various designs and durations) conducted with CERNEVIT as a component of parenteral nutrition.

Table 2: Additional Clinical Trials Adverse Reactions

System Organ Class (SOC)	Preferred MedDRA Term	Frequency[e]
METABOLISM AND NUTRITION DISORDERS	Vitamin A increased[a,b]	Unknown
	Retinol binding protein increased[b]	Unknown
HEPATOBILIARY DISORDERS	Transaminases increased	Unknown
	Isolated alanine aminotransferase increased[c]	Unknown
	Glutamate dehydrogenase increased	Unknown
	Blood alkaline phosphatase increased	Unknown
	Bile acids increased[d]	Unknown

[a] No symptoms of hypervitaminosis A were reported.

[b] Elevated plasma vitamin A levels have been reported in 8 of 20 patients receiving CERNEVIT in parenteral nutrition at day 45 of administration. From day 45 to day 90 of product administration the high values of vitamin A remained stable (maximum observed value of 3.6 µmol/L at day 90; normal values: 1 to 2.6 µmol/L). In addition, an average increase in retinol binding protein (RBP) was also identified. A maximum observed RBP value of 60 mg/L at day 90 (normal values: 30 to 50 mg/L), was reported.

[c] Isolated alanine aminotransferase increases was reported in the presence of inflammatory bowel disease. CERNEVIT was administered by intravenous injection in the absence of parenteral nutrition.

[d] An increase in total and individual bile acids including glycocholic acid has been reported to develop early in the course of parenteral nutrition administration in patients receiving CERNEVIT.

[e] The frequency either cannot be determined or the overall number of patients in the individual studies is too small to permit a valid estimation of frequency.

Post-marketing Adverse Reactions

The following adverse reactions have been reported in the post-marketing experience, listed by MedDRA System Organ Class (SOC), then by Preferred Term in order of severity, where feasible.
IMMUNE SYSTEM DISORDERS: 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.
NERVOUS SYSTEM DISORDERS: Dysgeusia (metallic taste)
CARDIAC DISORDERS: Tachycardia
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS: Tachypnea
GASTROINTESTINAL DISORDERS: Diarrhea
SKIN AND SUBCUTANEOUS TISSUE DISORDERS: Pruritus
HEPATOBILIARY DISORDERS: Gamma-glutamyltransferase increased
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS: Pyrexia, Generalized aching, Infusion site reactions, i.e., Burning sensation, Rash

Overdosage

Acute or chronic overdose of vitamin (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.

Effects on Ability to Drive and Use Machines

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

Storage

Store below 25°C, keep container in the outer carton. Protect from heat and light. To be used only as directed by medical practitioner. Reconstituted solution should be kept refrigerated (2° – 8°C) for no more than 24 hours.

Shelf Life

The unopened vial should be used before the expire date printed on the label.

Pharmaceutical Precautions

The product after reconstitution with water for injections should be used immediately or failing this be stored under refrigeration for no more than 24 hours.

Incompatibility Statement

- Additives may be incompatible with parenteral nutrition containing CERNEVIT.
- Do not add other medicinal products or substances without first confirming their compatibility and the stability of the resulting preparation.
- If co-administration of drugs that are incompatible at the Y-site is necessary, administer via separate IV lines.
- Vitamin A and thiamine in CERNEVIT 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 CERNEVIT.
- Folic acid stability can be impaired with increased calcium concentrations in an admixture.
- Numerous other incompatibilities between vitamins and other medicinal products, including certain antibiotics, and trace elements have been described.
- Refer to appropriate compatibility references and guidelines as needed.

HARUS DENGAN RESEP DOKTER.

Manufactured by: Valdepharm
France for **Baxter S.A.**, Belgium

Imported by: **PT KALBE FARMA Tbk. Bekasi – Indonesia**

Reg. No.: DKI0510700244A1

Presentation: Box of 10 vials @ 750 mg.

KALBE

BAXTER CONFIDENTIAL - INTERNAL USE ONLY	
Part Number: BE-30-03-784	Date: 06SEPT21 Proofread No.: 02
Designer: Z.B.	Page: 19 of 20
Colour Reference: BLACK	

BAXTER CONFIDENTIAL - INTERNAL USE ONLY	
Part Number: BE-30-03-784	Date: 06SEPT21 Proofread No.: 02
Designer: Z.B.	Page: 20 of 20
Colour Reference: BLACK	