SUMMARY OF PRODUCT CHARACTERISTICS

CERNEVIT

1. NAME OF THE MEDICINAL PRODUCT

Cernevit

Powder for solution for injection.

Intravenous administration.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial of powder contains:

Retinol palmitate	3500 IU
Cholecalciferol	220 IU
DL-α-tocopherol	10.20 mg
Ascorbic acid	125 mg
Cocarboxylase tetrahydrate	5.80 mg
Riboflavin dihydrated sodium phosphate	5.67 mg
Pyridoxine hydrochloride	5.50 mg
Cyanocobalamin	6 µg
Folic acid	414 µg
Dexpanthenol	16.15 mg
Biotin	69 µg
Nicotinamide	46 mg

equivalent to:

Vitamin A (Retinol)	3500 IU
Vitamin D3	220 IU
Vitamin E (α tocopherol)	11.20 IU
Vitamin C	125 mg
Vitamin B1 (Thiamine)	3.51 mg
Vitamin B2 (Riboflavin)	4.14 mg
Vitamin B6 (pyridoxine)	4.53 mg
Vitamin B12	6 µg
Folic Acid	414 µg
Pantothenic acid	17.25 mg
Biotin	69 µg
Vitamin PP (Niacine)	46 mg

Excipient with known effect:
Each vial contains 112.5 mg soybean lecithin.

Each vial contains 24 mg sodium (main component of cooking/table salt). This is equivalent to 1.2% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for solution for injection or infusion.
Orange yellow freeze-dried cake.

4. CLINICAL PARTICULARS

4.1. Therapeutic Indications

Vitamin supplementation in patients receiving parenteral nutrition.

Only for adults and children aged over 11 years of age.

4.2. Posology and Method of Administration

Posology

1 vial per day

Intravenous route exclusively.

Method of Reconstitution:

The single-dose vial of CERNEVIT is reconstituted by adding 5 ml of Sterile Water for Injection into the vial and gently mixing to dissolve the lyophilized powder. The obtained solution is yellow-orange in colour. The resultant solution should be administered by intravenous infusion. After reconstitution, CERNEVIT should be used immediately or stored under refrigeration (2-8°C) for no more than 24 hours. To minimize vitamin losses in parenteral nutrition admixtures, add the vitamins immediately prior to administration and complete administration within 24 hours. Discard any unused portion. Many parenteral vitamins are light sensitive and exposure to light should be minimized.

Notes
The total amount of powder in the vial (by weight)

The mean weight of the amount of powder in a Cernevit vial is 0.747g per vial with the approved limits of 0.710 g - 0.784 g according to the registered specifications for finished product release.

Volume after reconstitution

After reconstitution with 5 ml of solution, the final volume of the reconstituted Cernevit is 5.5 ml.

This medicinal product must not be mixed with other medicinal products except if compatibility and stability have been demonstrated.
Compatibility with solutions administered simultaneously through the same tubing must be checked.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solutions and container permit. Use of a final filter is recommended during administration of all parenteral solutions where possible.

From a microbiological point of view, the product should be used immediately after reconstitution. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user unless reconstitution has taken place under controlled and validated aseptic conditions.

Adults and Children aged 11 years and above
Adults and children aged 11 years and above should receive the contents of one vial (5 ml) per day.

4.3. Contraindications

CERNEVIT must not be used in:

- hypersensitivity to the active substances, especially vitamin B1 or to any of the excipients listed in section 6.1, 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 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 (See Section 4.8).

- 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, 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.

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 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 (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 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.

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.

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.

Vitamin K

Cernevit 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 Cernevit in patients at risk for vitamin B12 deficiency and/or when supplementation with Cernevit over several weeks is planned.

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

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.

Laboratory Test Interferences

Biotin

Biotin may interfere with laboratory tests that are based on a biotin/streptavidin interaction, leading to 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. When interpreting results of laboratory tests, possible biotin interference has to be taken into consideration, especially if a lack of coherence with the clinical presentation is observed (e.g. thyroid test results mimicking Graves' disease in asymptomatic patients taking biotin or false negative troponin test results in patients with myocardial infarction taking biotin). Alternative tests not susceptible to biotin interference should be used, if available, in cases where interference is suspected. The laboratory personnel should be consulted when ordering laboratory tests in patients taking biotin.

Ascorbic acid

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.

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.

Paediatric Use

Cernevit is indicated in paediatric patients over 11 years of age (see also Section 4.4: Hypervitaminosis A above).

Geriatric Use

In general, dosage adjustments for an elderly patient should be considered (reducing the dose and/or extending the dosing intervals) reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or drug therapy.

4.5. Interaction with Other Medicaments and Other Forms of Interaction

Interactions 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 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 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

Pernicious anaemia

The folic acid in Cernevit may obscure pernicious anaemia.

4.6. Fertility, Pregnancy and Lactation

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

Pregnancy
No safety data are available for Cernevit 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 Cernevit 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 Cernevit on the ability to operate an automobile or other heavy machinery.

4.8. Undesirable effects

Adverse drug reactions (ADRs) that occurred after administration of Cernevit are presented with their relative frequencies; these include ADRs documented in clinical trials and those from post-marketing reports. Cernevit was administered during 3 clinical trials to 267 adult patients requiring a parenteral vitamin supplement.

Frequencies of ARs are reported, using the following convention: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1000 to <1/100); rare (≥1/10000 to <1/1000); very rare (<1/10000); and unknown (cannot be estimated from the available data).

Clinical Trial and Post-Marketing Adverse Drug Reactions Reported for Cernevit:

System Organ Class	Preferred MedDRA Term	Frequency[1]
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	Unknown
Metabolism and nutrition disorders	Vitamin A increased[2,3], Retinol binding protein increased	Unknown Unknown
Nervous system disorders	Dysgeusia (metallic taste)	Unknown
Cardiac disorders	Tachycardia	Unknown
Respiratory, thoracic and mediastinal disorders	Tachypnea	Unknown
Gastrointestinal disorders	Nausea Vomiting Diarrhoea	Uncommon Uncommon Unknown
Hepatobiliary disorders	Transaminases increased, Isolated alanine aminotransferase increased[4], Glutamate dehydrogenase increased, Blood alkaline phosphatase increased, Bile acids increased[5] Gamma-glutamyltransferase increased	Unknown Unknown Unknown Unknown Unknown Unknown
Skin and subcutaneous tissue disorders	Pruritus	Unknown
General disorders and administration site conditions	Injection/Infusion Site Pain Pyrexia, Generalized aching, infusion site reactions, i.e., burning sensation, rash	Common Unknown Unknown Unknown

[1] 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.

[2] No symptoms of hypervitaminosis A were reported

[3] 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.

[4] 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.

[5] 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.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form

https://sideeffects.health.gov.il

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 (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, with the exception of Vitamin K.

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 lecithin, sodium hydroxide, hydrochloric acid.

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 Cernevit.

- 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.

6.3. Shelf Life

The expiry date of the product is indicated on the packaging materials.

After reconstitution with 5 ml water for injection should not be kept for more than 24 hours at 2-8°C.

Chemical and Physical in-use stability has been demonstrated for Cernevit for 24 hours when reconstituted with 5ml of Water for Injections and stored under refrigeration. From a microbiological point of view, the product should be used immediately. If not used immediately, in use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8°C, unless reconstitution/dilution etc has taken place in controlled and validated aseptic conditions.

6.4. Special Precautions for Storage

Do not store above 25ºC.
Keep the vial in the outer carton. Protect from heat and light.

For reconstituted product see sec. 6.3.

6.5. Nature and Contents of Container

Type I Ph.Eur. brown glass vial with an elastomer stopper, containing an orange-yellow sterile cake of powder;

Box of 1, 10 or 20 vials of lyophilised powder. Not all pack sizes may be marketed

6.6. Instructions for Use/Handling.

Aseptic conditions must be followed during reconstitution and when used as part of an admixture in parenteral nutrition.

Using a syringe, inject 5 ml of water for injections. The obtained solution is yellow-orange in colour.

Mix gently to dissolve the lyophilized powder.

Before transfer from the vial, Cernevit must be completely dissolved.

Do not use unless the reconstituted solution is clear, the original seal is intact and the container is undamaged.

After addition of Cernevit to a parenteral nutrition solution, check for any abnormal colour change and/or the appearance of precipitates, insoluble complexes, or crystals.

Mix the final solution thoroughly when Cernevit is used as an admixture in parenteral nutrition.

Single use only. Any unused portion of reconstituted Cernevit should be discarded and should not be stored for subsequent admixing.

Use of a final filter is recommended during administration of all parenteral nutrition solutions.

7. LICENSE HOLDER AND MANUFACTURER

License Holder

Remedix Care Ltd.
8 Haorgim St., Ashdod

Manufacturer

BAXTER S.A., BELGIUM
BOULEVARD RENE BRANQUART 80, B-7860 LESSINES, BELGIUM

8. REGISTRATION NUMBER

139-72-30602

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