PACKAGE LEAFLET: INFORMATION FOR THE PATIENT

CERNEVIT Powder for Solution for Injection or Infusion

Read all of this leaflet carefully before this medicine is given to you because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

In this leaflet:

Throughout this leaflet CERNEVIT Powder for Solution for Injection or Infusion will be called CERNEVIT.

1 What CERNEVIT is and what it is used for

CERNEVIT is a sterile powder for solution for injections or infusion. It contains 12 vitamins (see section 6).

CERNEVIT is used to give your daily requirement of vitamins straight into your blood. It is used when you cannot take enough food by your mouth. It is usually given with other things such as nutrition solutions and minerals.

2 What you need to know before CERNEVIT is given

You will not be given CERNEVIT if:

- you are allergic (hypersensitive) to the active substance or any of the ingredients of this medicine, especially vitamin B1 or soya protein or peanut protein (see Section 6, Contents of the pack and other information),
- you have too much of one of the vitamins in CERNEVIT stored in your body (called ‘hypervitaminosis’).

Do not have CERNEVIT if any of the above applies to you. If you are not sure talk to your doctor, nurse or pharmacist.

Warnings and precautions

Talk to your doctor, pharmacist or nurse before you are given CERNEVIT if:

- you are having vitamins, especially vitamin A (retinol) from other sources
- you have liver problems. Your doctor will do blood tests to check how well your liver is working. They will monitor the levels of certain 'enzymes' in your liver.
- you have kidney problems or are on dialysis. In this case your doctor will carefully monitor your fat-soluble vitamin levels. The fat-soluble vitamins are A, D, E and K
- you have a low body weight for your age, or do not receive enough nutrition from your diet
- you have inflammatory bowel disease (enterocolitis) or short bowel syndrome
- you are suffering from cystic fibrosis
- you are suffering from pressure ulcers (bed sores), wounds, burns
- you are suffering from pan excess of parathyroid hormone or from a cancer with associated elevated calcium levels in blood. Your doctor may monitor the levels of calcium and vitamin D.
- you have a peanut allergy. CERNEVIT contains soy-derived lecithin and should be used with caution in patients with peanut allergies due to potential cross-reactivity.

Your doctor will adapt the dose regimen based on you age and condition.

If you are not sure if any of the above applies to you, talk to your doctor, nurse or pharmacist before being given CERNEVIT.

Your doctor will make sure that:

- you are given additional vitamin K if you need it. CERNEVIT does not contain vitamin K
- your body has all that it needs for good health. If necessary, you may also be given minerals, amino acids (the building blocks of protein), fatty acids (the building blocks of fats), electrolytes (salts) and sugar solutions (such as glucose).

Other medicines and CERNEVIT

Before taking CERNEVIT, please tell you doctor, nurse or pharmacist if you are taking or have recently taken any other medicines, or getting administered new or different treatments in the course of parenteral nutrition. This includes medicines obtained without a prescription, including herbal medicines.

This is because some of the ingredients in CERNEVIT can affect the way some medicines work.

In particular tell your doctor, nurse or pharmacist if you are taking any of the following: Medicines to

- Treat Infections (Antibiotics)
- Thin the blood
- Prevent or treat seizures or convulsions
- Treat HIV infection
- Remove too much iron or copper from the body
- Treat tuberculosis
- Treat cancers
- Treat high blood pressure
- Treat rheumatoid arthritis
- Treat depression
- Treat acne or psoriasis
- Treat asthma or difficulty in breathing
- Treat Parkinson's disease

Before taking CERNEVIT, also tell you doctor, nurse or pharmacist if you are already on vitamins and are taking medications for any of the following conditions:

- Irregular heart beat
- Hardening of blood vessels
- Have an artificial heart valve or blood vessel.
- Epilepsy, bipolar disorder, facial pain
- Cancer
- Diabetes mellitus
- Anemia
- Contraception

Your doctor may monitor the levels of these medicines in your blood and may have to adjust their dose when you start or stop taking CERNEVIT.

Tests while you are having CERNEVIT

- CERNEVIT contains 69 micrograms biotin per vial (5 mL). If you are about to undergo laboratory testing you must tell your doctor or the laboratory personnel that you are taking or have recently taken CERNEVIT, because biotin may affect results of such tests. Depending on the test, the results may be falsely elevated or falsely low due to biotin. Your doctor may ask you to stop taking CERNEVIT before performing laboratory tests.

- CERNEVIT contains 125 milligrams ascorbic acid per vial (5 mL). Ascorbic acid may interfere with urine and blood glucose testing systems.

- CERNEVIT contains 414 micrograms folic acid per vial (5 mL). The folic acid in CERNEVIT may stop the detection of a problem called vitamin B_{12} deficiency associated megaloblastic anaemia. This is when you have a drop in red blood cells because your body cannot properly absorb vitamin B_{12} from your gut.

You should also be aware that other products that you may take, such as multivitamins or supplements for hair, skin, and nails could also contain biotin, folic acid or ascorbic acid and affect the results of laboratory tests. Please inform your doctor or the laboratory personnel, if you are taking such products.

Important information about some of the ingredients of CERNEVIT

This medicine contains 24 mg sodium (main component of cooking/table salt), per vial (5 mL), equivalent to 1.2% of the recommended maximum daily dietary intake of sodium for an adult.

Fertility, Pregnancy and breast-feeding

If you are pregnant or breast-feeding, think you might be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

Pregnancy

You may receive CERNEVIT during pregnancy if required, providing the indication and dosages are observed to avoid vitamin overdose.

Breast-feeding

The use of CERNEVIT is not recommended if you are breast-feeding. If you breast-feed whilst taking CERNEVIT there is a danger that your baby could get an overdose of vitamin A.

Fertility

No data are available on the effect of CERNEVIT on male or female fertility.

Use in Patients with liver disease

If you suffer from liver disease or from excessive alcohol consumption, tell your doctor. He/she will decide if you can have CERNEVIT or adjust the dose you will receive as necessary.

Use in Patients with kidney disease

If you suffer from kidney disease, tell your doctor. He/she will decide if you can have CERNEVIT or adjust the dose you will receive as necessary.

Paediatric Use

CERNEVIT can be used in paediatric patients over 11 years of age.

Geriatric Use

The dose will be adapted to your condition and needs.

3 How CERNEVIT is given

CERNEVIT will be given to you by a doctor or nurse.

How CERNEVIT is given

- The CERNEVIT powder will first be dissolved with a liquid such as 'sterile water for injection'. This will be mixed with a larger volume of fluid before it is given to you.
- It will be given into a vein as a drip (slow intravenous infusion) over at least ten minutes.
- CERNEVIT can also be added to other nutrition solutions. This mixed nutrition solution will be given to you as a drip into your vein.

The recommended dose

Your doctor will decide how much CERNEVIT you should be given. The amount you will be given depends upon your age, weight and the reason you are being given the medicine.

- Adults and children over 11 years: the recommended dose is one vial (small glass bottle) of CERNEVIT each day.
- Children under 11 years: not recommended.

If you are given too much

Your doctor or nurse will give you CERNEVIT so it is unlikely that you will be given too much. If you are worried that you have had too much, tell your doctor or nurse.

Signs of overdose of CERNEVIT are mostly the signs of overdose of vitamin A:

- Signs of sudden overdose of vitamin A include:
  - gastrointestinal disorders (nausea, vomiting),
  - nervous system disorders (headache, swelling of the optic nerve, convulsions) due to an increased pressure in your head,
  - psychiatric disorders (irritability),
  - skin disorders (delayed peeling of the skin).
- Signs of long-term overdose of vitamin A include:
  - headache due to an increased pressure in your head,

– bone disorders (tender or painful swellings at the ends of your limbs).

If you notice any of these signs of overdose, tell your doctor or nurse. They may stop your CERNEVIT infusion.

4 Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them. The following side effects may happen with this medicine.

The following side effect is common and could affect 1 to 10 users in 100:

- Pain at the site of injection

The following side effects are uncommon and could affect 1 to 10 users in 1,000:

- Feeling sick (nausea),
- being sick (vomiting)

The following side effects have been reported at an unknown frequency:

- Allergic reactions, with respiratory difficulties, chest pain, tightening of the throat, urticaria, rash, skin redness, abdominal discomfort, as well as cardiac arrest
- Severe allergic reaction (anaphylactic reaction)
- Increased levels of vitamin A and vitamin A carrier protein in blood
- Taste alteration (metallic taste)
- Accelerated heart rate
- Accelerated breathing rate
- Diarrhoea
- Increase in level of liver enzymes and bile acid
- Pruritus (itching)
- Fever, generalized soreness, reactions at the site of infusion such as burning sensation, rash.

If you show any symptom of an allergic reaction such as respiratory difficulties, chest pain, tightening of the throat, urticaria, rash, skin redness, abdominal discomfort, inform a doctor or nurse immediately. They will stop the infusion and conduct the necessary emergency measures.

Reporting of side effects

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via HPRA Pharmacovigilance, Earlsfort Terrace, IRL – Dublin 2.

Tel: +353 1 6764971; Fax: +353 1 6762517,

Website: www.hpra.ie; E-mail: medsafety@hpra.ie

5 How to store CERNEVIT

Because CERNEVIT is usually given in hospital it will be stored safely and correctly by the hospital staff. If you do need the storage conditions they are given below.

- Keep this medicine out of the sight and reach of children.
- This medicine will not be used after the expiry date that is stated on the label after 'EXP'. The expiry date refers to the last day of that month.
- Do not store above 25°C.
- Store in the outer carton in order to protect from light.
- CERNEVIT should not be used if the solution is not clear, the seal is broken or if the vial is damaged in any way.
- Once CERNEVIT has been mixed with water it should not be kept for more than 24 hours at 2 to 8°C, unless otherwise specified by your doctor.
- Partly used vials should not be used again. Any leftover CERNEVIT should be thrown away safely by a healthcare professional.
- All equipment used will be disposed of safely by a healthcare professional after use.

6 Contents of the pack and other information

What CERNEVIT contains

- The active substances are retinol palmitate (vitamin A) 3500 IU, colecalciferol (vitamin D3) 220 IU, DL-α-tocopherol (vitamin E) 10.20 mg, ascorbic acid (vitamin C) 125 mg, cocarboxylase tetrahydrate (vitamin B1) 5.80 mg, riboflavin dihydrated sodium phosphate (vitamin B2) 5.67 mg, pyridoxine hydrochloride (vitamin B6)
- 5.50 mg, cyanocobalamin (vitamin B12) 6 micrograms, folic acid 414 micrograms, dexpanthenol 16.15 mg, D-Biotin 69 micrograms, nicotinamide (vitamin PP) 46 mg per vial.

IU = International Units

mg = milligrams

- The other ingredients are glycine, glycocholic acid and soybean phosphatides. It may also contain small amounts of sodium hydroxide or hydrochloric acid for pH adjustment.

What CERNEVIT looks like and the contents of the pack

CERNEVIT is a powder for solution for injection or infusion. It is an orange-yellow cake of powder supplied in brown glass vials. It is packaged in cartons containing 1, 10 or 20 vials. Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturers

The Marketing Authorisation holder is:

Baxter Holding B.V. Kobaltweg 49, 3542CE Utrecht, Netherlands. Send all enquiries to this address.

CERNEVIT is made at:

Baxter S.A., Bd. R. Branquart 80, 7860 Lessines, Belgium

This leaflet was last revised in May 2019

For information about CERNEVIT or to request this leaflet in formats such as audio or large print please contact the Marketing Authorisation Holder: Tel: +44 1635 206345.

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TECHNICAL INFORMATION LEAFLET

CERNEVIT, Powder for Solution for Injection or Infusion

Pharmacist – please remove this section from leaflet

Presentation

Powder for solution for injection or Infusion in brown glass vials.

Each vial of powder contains:	Equivalent to:
Retinol palmitate 3500 IU	Vitamin A (Retinol) 3500 IU
Colecalciferol 220 IU	Vitamin D3 220 IU
DL-α-tocopherol 10.20 mg	Vitamin E (α tocopherol) 11.20 IU
Ascorbic acid 125 mg	Vitamin C 125 mg
Cocarboxylase tetrahydrate 5.80 mg	Vitamin B1 (thiamine) 3.51 mg
Riboflavin dihydrated sodium phosphate 5.67 mg	Vitamin B2 (riboflavin) 4.14 mg
Pyridoxine hydrochloride 5.50 mg	Vitamin B6 (pyridoxine) 4.53 mg
Cyanocobalamin 0.006 mg	Vitamin B12 0.006 mg
Folic acid 0.414 mg	Folic Acid 0.414 mg
Dexpanthenol 16.15 mg	Pantothenic acid 17.25 mg
D-Biotin 0.069 mg	Biotin 0.069 mg
Nicotinamide 46 mg	Vitamin PP (niacin) 46 mg

CERNEVIT also contains: Glycine, Glycocholic acid, Soybean phosphatides, Sodium hydroxide and Hydrochloric acid.

Indications

Supply of vitamins corresponding to the daily needs of adults and children over 11 years requiring multi-vitamin supplementation by the parenteral route when oral nutrition is contraindicated, impossible or insufficient (e.g. due to malnutrition, gastrointestinal malabsorption, parenteral nutrition, etc).

Dosage

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

Method of administration

Intravenous route: By slow intravenous injection (at least 10 minutes) or by infusion in a solution of 5% glucose or 0.9% sodium chloride solution for infusion.

Nature and Contents of Container

Type I Ph.Eur. brown glass vial, containing an orange-yellow sterile cake of powder, with an elastomeric stopper fitted with an aluminium closure.

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

Preparation of Solution

Using a syringe, inject 5 mL of water for injections into the vial. Mix gently to dissolve the powder. The obtained solution is yellow-orange in colour.

Do not use unless the reconstituted solution is clear, the original seal is intact and the container is undamaged. The reconstituted product is a clear yellow-orange solution. 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.

For single use only. Any unused portion of reconstituted CERNEVIT should be discarded and should not be stored for subsequent admixing.

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

CERNEVIT 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.

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.

Special Warnings and Special 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.
- 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.
- 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.

Caution should be exercised when administering CERNEVIT to patients with symptomatic hypercalcemia that results from excess vitamin D levels. Due to the risk of hypercalcemia complication, CERNEVIT should be administered with caution to patients suffering from primary hyperparathyroidism or malignancy with secondary hypercalcemia. Administration of calcium and vitamin D to these patients should be closely monitored.

- 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.
- 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.

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

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.

Interference with clinical laboratory tests

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.

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

This medicinal product contains 24 mg (1.04 mmol) sodium, per vial (5 mL), equivalent to 1.2% of the WHO recommended maximum daily intake of 2 g sodium for an adult. This is to be taken into consideration for patients 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.

Interaction with Other Medicaments and Other Forms of Interactions

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. Plasma concentrations of anticonvulsants should be monitored with concurrent use of folate. Clinical surveillance, eventually plasma

level monitoring, and, if necessary, adjustment of the dose of the anticonvulsant may be necessary during folic supplementation and after it is withdrawn.

- 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 (also see 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

<u>Drugs that Bind to alpha1-Acid Glycoprotein (AAG):</u>

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

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.

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.

Incompatibilities

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.

Storage and Stability

Do not store above 25°C. Keep the vial in the outer carton. Keep this medicine out of the sight and reach of children. *Shelf life unopened: 2 years.*

Shelf life after reconstitution for intravenous administration: Chemical and Physical in-use stability has been demonstrated for CERNEVIT for 24 hours at 25°C when reconstituted with 5 mL of Water for Injections.

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.

Marketing Authorisation Holder

Baxter Holding B.V. Kobaltweg 49, 3542CE Utrecht, Netherlands

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For information about CERNEVIT or to request this leaflet in formats such as audio or large print please contact the Marketing Authorisation Holder Tel: +44 (0)1635 206345.