

CERNEVIT

CERNEVIT is a multivitamin preparation, lyophilised, sterile powder, for reconstitution in 5mL of Water for Injection or other compatible parenteral fluids.

COMPOSITION

Content of lyophilisate in each vial.

<i>Active Ingredients</i>	<i>Corresponding to</i>		
Retinol (present as retinyl palmitate)	3500IU	Vitamin A	3500IU
Colecalciferol	5.5µg	Vitamin D ₃	5.5µg
dl-α-tocopherol	10.20mg	Alpha tocopherol (Vitamin E)	11.20IU
Asorbic acid	125mg	Vitamin C	125mg
Cocarboxylase tetrahydrate	5.80mg	Thiamine (Vitamin B ₁)	3.51mg
Riboflavin sodium phosphate	5.67mg	Riboflavin (Vitamin B ₂)	4.14mg
Pyridoxine hydrochloride	5.50mg	Pyridoxine (Vitamin B ₆)	4.53mg
Cyanocobalimin	6µg	Vitamin B ₁₂	6µg
Folic acid	414µg	Folic acid	414µg
Dexpanthenol	16.16mg	Dexpantothenic acid	17.25mg
d-Biotin	69µg	Biotin	69µg
Nicotinamide	46mg	Niacin (Vitamin PP)	46mg
<i>Excipients:</i>			
Glycine	250mg		
Glycocholic acid	140mg		
Lecithin	112.5mg	Lecithin (Soybean)	112.5mg
Sodium hydroxide 10%	qs		
1M hydrochloric acid	qs pH 5.9		

The active ingredients in CERNEVIT are water-soluble and fat-soluble vitamins, which are well characterised. The Glycine component is included in the formulation as an excipient in order to facilitate the reconstitution of the lyophilised product with Water for Injection.

DESCRIPTION

CERNEVIT is a sterile dosage form for injection containing nine water-soluble and three fat-soluble vitamins (Vitamin K is not included in Cernevit), using mixed micelles (glycocholic acid and lecithin) as a solubilising agent. It is presented as a lyophilised, orange-yellow, sterile powder. That is to be reconstituted with 5mL of Water for Injections or other parenteral fluids, (e.g. as 0.9% Sodium chloride, 5% Glucose or nutritional mixtures), prior to administration by parenteral route.

PHARMACOLOGY

A general mode of action of CERNEVIT is to provide a balanced physiological effect mediated by the water-soluble and fat-soluble vitamins in adults and children. Composition and proportion of each vitamin correspond to the recommendations of the American Medical Association, Food and Drug Administration and Food and Nutrition Board in parenteral nutrition.

Pharmacodynamics

Each vitamin has its specific function in regulating metabolic process in living cells. As CERNEVIT contains more than one active ingredient, it has multifactorial physiological effects. Some functions are performed by one vitamin, such as vitamin A, which is necessary for proper functioning of the retina and the integrity of epithelial cells.

Insufficient retinol (Vitamin A) supplies for the formation of rhodopsin lead to a night blindness syndrome. Other fat-soluble vitamins (Vitamin D and E) are involved in different functions. That is, Vitamin E preserves the essential cell constituents by virtue of its anti-oxidant property, whilst Vitamin D exerts its physiological effect via a hormone-like mode of action on bone formation and mineral homeostasis.

An excess intake of fat-soluble vitamins, such as Vitamin A, may lead to a toxic effect because of its accumulation in the body. This is caused by a slow metabolism and excretion of this vitamin. More than 90% of Vitamin A body supply is stored in the liver and this reserve is usually sufficient for several months to a year. Thus, frequent replacement of Vitamin A is not needed, in contrast to water-soluble vitamins (Vitamin B-complex and Vitamin C), which require a continuous replacement due to their fast excretion from the body.

Water-soluble vitamins act as co-enzymes, mainly in energy metabolism. The B-complex vitamins are necessary for conversion of carbohydrate, protein and fat into tissue and energy. That is, biotin and niacin function as a component of carboxylase enzymes in those metabolic reactions, whilst Vitamin C is involved in collagen formation and tissue repair. Tetrahydrofolic acid, the co-enzyme form of the vitamin, serves as an acceptor and a donor of one carbon unit in amino acid and nucleotide metabolism. Excess intake of water-soluble vitamins is excreted readily by the kidney in the urine by virtue of a high solubility of the parent and their metabolites

in water, thereby accumulations rarely take place. Thus, toxicity is less often experienced with water-soluble vitamins than with fat-soluble vitamins.

Pharmacokinetics

The mode of administration of CERNEVIT is by injectable route, thus the bioavailability of this product is considered 100% as it is directly provided into systemic circulation.

INDICATIONS

CERNEVIT is indicated in adults and children over 11 years of age requiring parenteral multi-vitamins supplementation to correct or prevent vitamin deficiencies when oral administration is contraindicated, impossible or insufficient. This product does not contain vitamin K, which may be given separately if required.

CONTRAINDICATIONS

CERNEVIT is contraindicated in patients with pre-existing hypervitaminosis or known hypersensitivity to any of the active ingredients, in particular patients with hypersensitivity to thiamine (Vitamin B₁). Thus, CERNEVIT should not be injected to patients with pre-existing intolerance to thiamine. Similarly, this product should not be administered to patients with impaired hepatic function.

Cernevit should not be administered to those suffering from hyperparathyroidism due to hypercalcaemic complications.

PRECAUTIONS

General

Anaphylactic reactions may occur in allergic subjects who are susceptible to thiamine (Vitamin B₁) and nicotinamide components of this product. Mild allergic reactions such as sneezing or mild asthma are warning signs that further injection may give rise to anaphylactic shock.

Daily vitamin requirements must be calculated in order to avoid overdose and toxic effects, in particular with fat soluble vitamins, such as Vitamin A. Caution should be exercised when administering CERNEVIT to patients who may be receiving Vitamin A from other sources.

The recommended Dietary Intakes (RDI) of Vitamin A in pregnant and lactating women as recommended by the NH&MRC is 2500IU (750mcg retinol equivalents). CERNEVIT IV contains 3500IU vitamin A, administered by intravenous route, thus the use of this product in

pregnant or lactating women is not recommended. Teratogenic effects have been observed in isolated cases with a dose vitamin A over 10,000IU per day.

Following intravenous bolus injection, a moderate rise in SGPT transaminases has been noted in some patients with active inflammatory enterocolitis. The increased levels are rapidly reversible following the cessation of the treatment. It is recommended to monitor transaminase levels in patients of this type.

Due to glychocolic acid content, repeated and prolonged administration in patients with jaundice of hepatic origin or severe biochemical evidence of cholestatis requires careful monitoring of liver function.

Also in the case of impaired kidney function, fat-soluble vitamin levels should be carefully monitored.

CERNEVIT does not contain Vitamin K. If the patient requires this vitamin, it should be administered separately.

Carcinogenicity, mutagenicity, and teratogenicity

No carcinogenicity, mutagenicity or fertility studies have been performed with CERNEVIT. In a single test for mutagenicity in bacteria, heat-degraded mixed micelles, a solubilising agent in the product, were not mutagenic.

Use in Pregnancy (Category D)

Animal reproduction studies have not been performed with CERNEVIT. However, embryofoetal toxicity studies were carried out in rats and rabbits using heat-degraded mixed micelles, a solubilising agent used in CERNEVIT. In rabbits, maternotoxic doses of heat-degraded mixed micelles led to an increased abortion rate, but there were no adverse effects on the foetus.

Vitamin A is classified as category D in the Australian Categorisation of risk of drug in pregnancy. The amount of vitamin A in this product is below the RDA adopted by the FDA/USA, but above that recommended by the NH&MRC. This product has not been formally assessed in human pregnancy, therefore use of this product in pregnancy is not recommended. Teratogenic effects have been observed in isolated cases with doses of Vitamin A over 10,000IU/day.

Use in Lactation

It is not known if this drug is excreted in breast milk, but as many vitamins are, the use of this product in lactating women is not recommended.

Interaction with Other Drugs

In an *in vitro* study using human serum, therapeutic concentration of glycocholic acid increased the unbound fraction of drugs known to bind to a1-acid glycoprotein by 50-80%. Patients receiving drugs that bind to a1-acid glycoprotein should be closely monitored for increases in response to these drugs, e.g. propranolol, prazosin and quinidine.

The dosage of drugs known to be influenced by folic acid, for example phenytoin (Dilantin), must be carefully monitored. Folic acid may obscure pernicious anaemia.

Folic acid may increase the metabolism of some antiepileptics, such as phenobarbitol, phenytoin and primidone. Pyridoxine can reduce the effect of levo-dopa. Bleomycin can be inactivated by ascorbic acid and riboflavin. Several vitamins can decrease the effectiveness of antibiotics, such as tetracycline.

It has been reported that PVC bags and plastic tubing delivery system absorb fat-soluble vitamins onto the plastic surface, in particular vitamin A in the form of pure vitamin A or vitamin A acetate, which are highly prone to this phenomenon. The use of vitamin A palmitate and 'mixed micelles' as solubilising agents in the formulation of CERNEVIT reduces the absorption of fat-soluble vitamins onto plastic bag as a result of the high rate of vitamin A palmitate being trapped into the micelles cages. Using non-PVC bags may prevent this interaction. Some of the vitamins, especially A, D and riboflavin are light sensitive. Thus, light protection is recommended during administration of an IV infusion admixture containing CERNEVIT, by wrapping the container with an adequate light-barrier cover.

ADVERSE EFFECTS

Anaphylactic reactions have been reported following intravenous doses of thiamine. There have been reported very rare events of anaphylactic reaction following IV injection of CERNEVIT over 1 – 4 minutes. Giant urticaria has been very rarely reported, as well as rash. Transient rises in SGPT transaminases have been observed after bolus injection in patients with active inflammatory enterocolitis. Individuals susceptible to the effects of nicotinamide may experience flushing, itching or burning of the skin.

DOSAGE AND ADMINISTRATION

Dosage

Adults and children aged over 11 years: 1 vial/day reconstituted with Water for Injection (5mL) or other compatible IV solutions (5mL) as described under Administration and Reconstitution.

Administration and Reconstitution

CERNEVIT is a sterile preparation. Thus, aseptic procedure must be applied throughout the administration and reconstitution. The single dose vial of CERNEVIT is reconstituted by adding 5mL of sterile Water for Injection or other intravenous fluids (0.9% Sodium Chloride Injection or 5% Glucose Injection). Five millilitres (5mL) of diluent should be added by means of sterile syringe into the vial and gently mixed to dissolve the lyophilised powder. The entire volume of the resultant solution should then be administered by slow Intravenous Injection (at least over 10 minutes) or further diluted for intravenous infusion. After reconstitution, CERNEVIT should be used immediately or stored at 2°C to 8°C for no more than 24 hours.

Overdose

There is little data concerning the overdosage of CERNEVIT.

The signs of overdose of CERNEVIT are mostly those resulting from administration of excessive doses of vitamin A:

- Clinical signs of acute overdose of Vitamin A (doses exceeding 150,000IU): gastrointestinal disorders, headache, raised intracranial pressure, papilloedema, psychiatric disorders, irritability, or even convulsions, delayed generalised desquamation.
- Clinical signs of chronic intoxication (prolonged vitamin A supplementation with supraphysiological doses in non-deficient subjects): raised intracranial pressure, cortical hyperostosis of long bones and premature epiphyseal fusion. The diagnosis is generally based on the presence of tender or painful subcutaneous swellings in the extremities of the limbs. X-rays demonstrate diaphyseal periosteal thickening of the ulna, fibula, clavicles and ribs.
- Action to be taken in the event of acute or chronic overdose: stop administration of CERNEVIT, reduce calcium intake, increase diuresis and rehydrate.

Hypercalcaemia occurs as a result of Vitamin D hypervitaminosis. Symptoms of hypercalcaemia include nausea, vomiting, polyuria, anorexia, weakness, apathy, thirst and constipation. Chronic overdose can lead to vascular and organ calcification. Chronic overdoses can lead to vascular and organ calcification as a result of hypercalcaemia. Treatment should consist of stopping all intake of calcium and vitamin D and rehydration.

In cases of suspected overdose, symptomatic and supportive therapy should be instituted as appropriate, and further administration of the product discontinued.

Given the doses of these vitamins contained in CERNEVIT, it is unlikely that, used as directed, toxicity would occur, however, care must be taken if patients are receiving any additional supplementation from other sources.

Contact the Poisons Information Centre for advice on management of overdosage.

PRESENTATION

Lyophilised sterile powder in a brown glass vials, with elastomer closures and crimped by an aluminium cap. Packs available in 1's, box of 10 and box of 20 ampoules.

Storage conditions

Store below 25°C. Protect from light. Do not freeze. After reconstitution, the reconstituted product should be used immediately, or failing this, it should be stored at 2°C to 8°C for no more than 24 hours. Contains no antimicrobial agent. The product is for single use in one patient only. Discard any unused portion of the reconstituted solution.

Note: see Precautions during infusion, light protection should be obtained by wrapping the container with an adequate light barrier.

Shelf life

2 years.

MEDICINES CLASSIFICATION

General Sale Medicine.

NAME AND ADDRESS

CERNEVIT is supplied in New Zealand by:

Baxter Healthcare Ltd
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Mt Wellington
Auckland 1060

CERNEVIT supplied in Australia by:

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Please refer to the Medsafe website (www.medsafe.govt.nz) for most recent data sheet.