PROFESSIONAL INFORMATION

Complementary Medicine Health Supplement

This unregistered medicine has not been evaluated by SAHPRA for its quality, safety or intended use.

SCHEDULING STATUS: S0

1 NAME OF THE MEDICINE

Cal-C-Vita Immuno Pro Effervescent Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

This product is a multivitamin and mineral preparation, containing seven (7) vitamins and four (4) trace elements.

Each effervescent tablet contains the following active ingredients:

Ingredient Name	Quantity
Vitamin A (Retinyl palmitate)	2333 IU
Vitamin B_6 (Pyridoxine hydrochloride)	6,5 mg
Folic acid	400 µg
Vitamin B_{12} (Cyanocobalamin)	9,6 µg
Vitamin C (Ascorbic acid)	1 000 mg
Vitamin D3 (Cholecalciferol)	400 IU
Vitamin E (DL-α-Tocopheryl acetate)	45 mg
Zinc (Zinc citrate trihydrate)	10 mg
Copper (Copper citrate)	64 µg
Iron (Ferric pyrophosphate)	5 mg
Selenium (Sodium selenite)	110 µg

Sugar free.

Contains sweeteners: Acesulfame potassium 20 mg and Aspartame 40mg.

For full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Effervescent tablet.

Pale yellow orange, speckled, flat, bevelled edges, with odour of oranges.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Cal-C-Vita ImmunoPro Effervescent Tablets is a combination of vitamins and minerals designed to support the maintenance of a healthy immune system for overall health.

4.2 Posology and method of administration

Posology

For oral use.

The recommended intake for adults and children above 12 years of age is one effervescent tablet a day dissolved in glass (i.e. approximately 200 ml) of water.

4.3 Contraindications

- Hypersensitivity to any of the active substances or to any of the excipients listed in section 6.1.
- Cal-C-Vita ImmunoPro is not suitable for people with hemochromatosis or renal disorders. This includes patients on dialysis.
- Cal-C-Vita ImmunoPro Effervescent Tablets must not be taken by patients with phenylketonuria since the product contains a source of phenylalanine (aspartame).
- This product is not intended for use during pregnancy and lactation.
- Iron and/or copper metabolism disorders
- Hypervitaminosis A
- Hypervitaminosis D
- Hypercalcaemia
- Nephrolithiasis or history of nephrolithiasis
- Hyperoxaluria
- Renal Insufficiency

- Concomitant treatment with vitamin A, retinoids, beta-carotene, or the synthetic isomers such as isotretinoin and etretinate. (see section 4.5)

4.4 Special warnings and precautions for use

Do not exceed the labelled dose. Acute and chronic overdose increases the risk of adverse effects. Allowance should be made for intake of the vitamins and minerals from all other sources including fortified foods, dietary supplements, and concomitant medications (see section 4.9).

Individuals receiving other single vitamins or multivitamin preparations, any other medication or those under medical care should consult a health care professional before use of the product (see sections 4.5).

Overdose of vitamin C in individuals with glucose-6-phosphate dehydrogenase deficiency (> 3 g in children and > 15 g in adults) has been associated with haemolytic anaemia (see section 4.9).

Concomitant treatment with vitamin D analogues should be avoided due to risk of hypervitaminosis D and/or hypercalcaemia. If concomitant use is deemed essential, the serum and urinary levels of calcium must be regularly monitored (see section 4.5).

Separate intake of the product from other medications by four (4) hours unless otherwise specified (see section 4.5).

Vitamin C may interfere with laboratory tests resulting in false readings. Inform you physician or health care professional when taking this product and laboratory tests are planned (see section 4.5).

Vitamin C may interfere with testing kits and meters that measure glucose levels resulting in false readings. Refer to the package insert of the testing kit or the meter for guidance (see section 4.5).

Cal-C-Vita ImmunoPro Effervescent Tablets contain 302,64 mg of sodium per tablet. To be taken into consideration by patients on a controlled sodium diet.

4.5 Interaction with other medicines and other forms of interaction

Manifold potential interactions are reported in the literature for the single ingredients, thus individuals receiving any other medication, dietary/food supplements, or those under medical care should consult a physician or health care professional before use of the product. When used as recommended no specific interactions are expected.

Drug interactions

Active Ingredient	Drug	Description
Vitamin C	Desferrioxamine	Vitamin C may enhance tissue iron toxicity, especially in the heart, causing cardiac decompensation.
	Cyclosporine	Antioxidant supplementation including vitamin C may reduce cyclosporine blood level.
	Disulfiram	Chronic or high doses of vitamin C may interfere with the effectiveness of the disulfiram.
	Indavinir	High-dose vitamin C may significantly reduce the serum concentration of indinavir, which may interfere with the effectiveness of indavinir.
	Warfarin	High dose vitamin C may interfere with the effectiveness of warfarin.
Vitamin B_6	Levodopa	Pyridoxine enhances the metabolism of levodopa, reducing its anti-parkinsonism effects. However, this interaction does not occur when carbidopa is in combination with levodopa (i.e. Sinemet®).
Folic Acid	Methotrexate	Folic acid supplementation may reduce the effectiveness of methotrexate in the treatment of acute lymphoblastic leukemia, and theoretically, the efficacy in the treatment of other cancers.
Vitamin A	Retinoids*	Vitamin A supplementation must be avoided during treatment with vitamin A, retinoids, beta-carotene, and/or the synthetic isomers due to increased risk of vitamin A toxicity. Synthetic isomers include isotretinoin, etretinate, acitretin, and bexarotene.
Vitamin D3	Vitamin D analogues	Concomitant treatment with vitamin D analogues should be avoided due to increased risk of hypervitaminosis D and/or hypercalcaemia. Vitamin D analogues include ergocalciferol and calcitriol. If deemed essential, serum and urine calcium levels should be monitored.
Vitamin A and vitamin D	Cholestyramine	Gastro-intestinal absorption of vitamin A and vitamin D is decreased with simultaneous administration. Separate intake of the product and these medications by four hours, unless otherwise specified, will minimize risk for any interaction.
Vitamin A, Vitamin D, and Vitamin E	Orlistat	Gastro-intestinal absorption of vitamin A, vitamin D, and vitamin E is decreased with simultaneous administration. Separate intake of the product and these medications by four hours, unless otherwise specified, will minimize risk for any interaction.
Copper, Iron, Selenium, and Zinc	Mineral Oil	Polyvalent cations, such as copper, iron, selenium, and/or zinc, form complexes with certain substances resulting in decreased absorption of both substances. Separate intake of the product and these medications by 4 hours, unless otherwise specified, will minimize risk for this interaction.
	Tetracycline antibiotics	
	Quinolone antibiotics	
	Penicillamine	
	Biphosphonates	
	Levothyroxine	
	Methyldopa	
	Mycophenolate mofetil	

Active Ingredient	Drug	Description
	Eltrombopag	
***Major**		

Lab interactions

Because vitamin C is a strong reducing agent (i.e. electron donor), it can cause chemical interference in laboratory tests that involve oxidation-reduction reactions, such as the analyses of glucose, creatinine, uric acid, and inorganic phosphates in urine, serum and of occult blood in faeces. Using specific tests that are not dependent on reducing properties or discontinuing extra dietary vitamin C will avoid any undesirable interference. Refer to the manufacturer's information to determine if ascorbic acid interferes with the test.

Vitamin C may interfere with tests that measure urinary and blood glucose resulting in false readings, although it has no effect on blood glucose levels. Refer to the package insert of the meter or testing kit to determine if vitamin C (ascorbic acid) interferes and guidance for accuracy in readings.

4.6 Fertility, pregnancy and lactation

Fertility

There is no evidence suggestive that normal endogenous levels of the vitamins and minerals in the product cause adverse reproductive effects in humans.

Pregnancy

This product is not intended for use during pregnancy and lactation. since there are no sufficient controlled human studies assessing the risk of product treatment during pregnancy or lactation, the product should only be used in pregnancy or lactation if deemed essential by the physician. The labelled dose should not be exceeded since chronic overdose might be harmful to the foetus and neonate. Allowance should be make for intake of the vitamins and minerals from all other sources.

Breastfeeding

The vitamins and minerals in the product are excreted into breast milk. This should be taken into consideration.

4.7 Effects on ability to drive and use machines

The product has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

The listed adverse reactions have been identified during post-approval use of the product. Because these reactions are reported voluntarily, it is not possible to estimate their frequency.

Gastrointestinal disorders

Diarrhoea, nausea, vomiting, gastrointestinal and abdominal pains.

Immune system disorders

Allergic reaction, anaphylactic reaction, anaphylactic shock.

Hypersensitivity reactions with respective laboratory and clinical manifestations include asthma syndrome, mild to moderate reactions potentially reported. If an allergic reaction occurs, treatment must be stopped and a health care professional consulted affecting skin, respiratory tract, gastrointestinal tract, and cardiovascular system, including symptoms such as rash, urticaria, allergic edema and angioedema, pruritus, cardio-respiratory distress, and, severe reactions, including anaphylactic shock.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the **"6.04 Adverse Drug Reactions Reporting Form"**, found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8 or you can report the side effects directly to Bayer Pharmacovigilance Department by sending and email to zapv@bayer.com or via the Bayer website (www.bayer.co.za). By reporting side effects, you can help provide more information on the safety of Cal-C-Vita ImmunoPro Effervescent Tablets.

4.9 Overdose

General manifestations of overdose may include abrupt onset of headache, confusion, and gastrointestinal disturbances such as constipation, diarrhoea, nausea, and vomiting. If such symptoms occur, the product should be stopped and a health care professional consulted.

Acute or chronic overdose of the product may cause hypervitaminosis A and D, as well as toxicity associated with the other active ingredients in the product including vitamin C, zinc, selenium, iron, and copper.

Specific clinical signs and symptoms, laboratory findings, and consequences of overdose are highly diverse, dependent on an individual's susceptibility, and surrounding circumstances.

Specific clinical manifestations may include the following:

Vitamin C

Acute or chronic overdose of vitamin C (> 2g/day in adults) may significantly elevate serum and urinary oxalate levels. In some instances, this results in hyperoxaluria, calcium oxalate crystalluria, calcium oxalate deposition, kidney stone formation, tubulointerstitial nephropathy, and acute renal failure. Individuals with renal disorders may be more susceptible to these effects of vitamin C toxicity at lower doses. Use in these individuals is contraindicated (see section 4.3).

Overdose of vitamin C in individuals with glucose-6-phosphate dehydrogenase deficiency (> 3 g / day in children and > 15 g / day in adults) may result in oxidative haemolysis or disseminated intravascular coagulation.

Vitamin A

Abrupt onset of headache, or dermal changes, and diplopia may be one of the earliest signs of retinal toxicity. Excessive intake of vitamin, the synthetic isomers isotretinoin and etretinate, or beta-carotene causes fatigue, irritability, anorexia, gastrointestinal disturbances, skin and hair changes (e.g. erythema and pruritus). Other symptoms from a single massive dose consist of gastro-intestinal symptoms (abdominal pain, nausea, vomiting), and pseudotumor cerebri (increased intracranial pressure with the symptoms: headache, dizziness, sluggishness, papilla oedema, in addition to a transient bulging fontane in infants), followed within a few days by a generalised desquamation of the skin.

Chronic toxicity syndrome is characterized by bone and joint pain, hyperostosis, hair loss, dryness and fissures of the lips, pruritus, anorexia, benign intracranial hypertension, low grade fever, weight loss and hepatosplenomegaly. Hepatotoxic reactions are present in about half the cases of chronic hypervitaminosis A. In addition to clinical signs such as hepatosplenomegaly, spider naevus, leukonychia, palmar erythrosis and jaundice, hepatic transaminases (aspartate and alanine aminotransferases) are elevated. Elevation of alkaline phosphatase may be prominent and cholestasis with hyperbilirubinemia may be present. A reversible portal hypertension syndrome with ascites may occur. Generally the signs and symptoms of retinol toxicity rapidly resolve once intake has been ceased.

Intake of vitamin A from all sources (>10, 000 IU/day) is teratogenic. Concomitant treatment with vitamin A analogues is contra-indicated.

Vitamin D

Chronic ingestions of vitamin D in excess of 4 000 IU/day (100 µg/day) can result in toxicity Many of the effects of chronic vitamin D toxicity are due to induced hypercalcaemia. Symptoms may include anorexia, nausea, vomiting, and weight loss.

Maternal hypercalcemia, possibly caused by excessive vitamin D intake during pregnancy, has been associated with hypercalcemia in neonates, which may lead to supravalvular aortic stenosis syndrome, the features of which may include retinopathy, mental or growth retardation, strabismus and other effects.

Vitamin B_6

The effect of pyridoxine overdose is a sensory axonal neuropathy. Central effects have also been described. Neuropathy has been most commonly reported after chronic ingestion of 200 to 6000 mg/day for months or years. The neuropathy gradually improved in all cases, following removal of pyridoxine. Irreversible destruction of sensory ganglion cells (neuronopathy) may also occur after a single extremely large parenteral dose, but the exact toxic amount is not well documented in humans.

Iron

Vomiting, hematemesis, abdominal pain, diarrhoea, haematochezia, lethargy, shock, acidosis and coagulopathy may occur when high doses are ingested (20 to 60mg). Necrosis to the gastrointestinal tract occurs from the direct effect of iron on the mucosa. Severe gastrointestinal haemorrhagic necrosis with large loses of fluid and blood contribute to shock. Free iron and ferritin produce vasodilatation that may also contribute to shock.)

Selenium

At high doses (>280 mcg/day in children > 12 years of age and 900 mcg/day in adults) selenium causes toxicity. Manifestations include hair loss, abnormal nails, dermatitis, peripheral neuropathy, nausea, diarrhoea, fatigue, irritability, and a garlic odour of the breath. Toxic levels of plasma selenium are not well defined.

Copper

Acute ingestion of copper (120 mg/kg)) can cause irritation, severe nausea and vomiting, salivation, abdominal pain, epigastric burning, haemolysis, gastrointestinal bleeding with haemorrhagic gastritis, hematemesis and melena, anaemia, hypotension, jaundice, seizures, coma, shock and death. Hepatic and renal failure may develop several days after acute ingestion. Methemoglobinemia may rarely occur.Copper may produce a metallic or sweet taste.

Zinc

Zinc overdose can cause irritation and corrosion of the gastrointestinal (GI) tract, acute renal tubular necrosis, and interstitial nephritis.

If overdose with the product is suspected, intake should be stopped and a health care professional consulted for treatment of clinical manifestations.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacological classification: category D 34.12 (Multiple substance formulation).

Multivitamins with minerals (incl. combinations with trace elements) constitute a distinct pharmacotherapeutic group under the ATC code **A11AA**.

This product is a combination of selected vitamins and trace elements required for growth, development, health maintenance, general well- being, disease prevention and immune function. This product is specifically indicated for the stimulation of the immune functions and the restoration of resistance to infection in situations of inadequate micronutrients supply (Wintergerst et al, 2007, Maggini et al, 2008; Maggini, 2010 and references therein).

Vitamins, minerals and trace elements are essential active agents for maintaining the physiological functions of the organism. The human organism cannot synthesize them and is therefore dependent on a continuous exogenous supply. Vitamins are essential to all metabolic pathways and are crucial to their well-balanced co-ordination. Thus the combination of different vitamins, minerals and trace elements into one product is required by the extensive co-operative interactions of these micronutrients such as mutual interdependence in their activation, metabolism and activity and in their biochemical and physiological co- operation in different metabolic pathways. The oral application

of combinations of vitamins and minerals is the natural way of supply, as they also appear as such in natural foodstuff.

This product is a combination of selected vitamins and trace elements required for growth, development, health maintenance, general well- being, disease prevention and immune function. This product is specifically indicated for the stimulation of the immune functions and the restoration of resistance to infection in situations of inadequate micronutrients supply.

The product is suitable for elderly individuals who are at risk of developing micronutrient deficiency and experience at the same time a decline in their immune functions. Aged individuals are more sensitive to infections than younger adults: infection is a common problem among elderly, who are 2 to 10 times more likely to die of infection than their younger counterparts.

The immune system protects the body against infectious agents such as bacteria, virus, fungi, parasites, and other toxins, and defends against infections via three different components: physical barriers (e.g. skin, mucosa), immune cells (e.g. lymphocytes, macrophages), and antibodies. Immune defence consists of a highly complex biological response which involves cellular proliferation, enhanced protein synthesis and inflammatory mediators production as well as physiological changes.

The generation of reactive oxygen species is part of the physiological function of cells involved in host defence such as granulocytes or macrophages, especially during chemotactic locomotion, phagocytosis and microbicidal activity. Also gene expression is modulated by reactive oxygen species which are released into the cytoplasm in response to ligand-receptor interactions on the membranes of immune cells, and regulating the biosynthesis of antibodies or cytokines. Reactive oxygen species are further involved in the process of apoptosis. The immune system is particularly vulnerable to oxidative stress, since immune cells rely on cell-cell communication via membrane-receptors.

The profound interactions among nutrition, infection, and health have been recognized for many decades. Several vitamins and minerals have been demonstrated in either animal or human studies to be required at appropriate amounts for the immune system to function efficiently. These micronutrients include vitamin A, vitamin D, vitamin 86, vitamin 812, folate, vitamin C, vitamin E, zinc, copper, iron, and selenium. Insufficient intake of multiple nutrients is more frequently occurring than a single deficiency due to poor nutrition, especially in developing countries, but vitamin/mineral under-nutrition is also observed in industrialized countries, especially among the elderly, in people

with eating disorders, in smokers and individuals with chronic alcohol abuse, in patients with certain diseases, and during pregnancy and lactation.

Under-nutrition and nutrient deficiency impair the proper functioning of the immune system, suppressing various immune functions which are critical determinants of host resistance. As a consequence, under- nourished or vitamin/mineral-deficient individuals have been shown to be more susceptible to infections. Studies have shown that supplying the deficient nutrients can restore immune function and restore resistance to infections, besides improving the overall micronutrient status of the individuals. Vitamins A, C, E and the trace element zinc assist in enhancing the epithelial barrier function. The vitamins A, B6, B12, C, D, E, folic acid and the trace elements iron, zinc, copper and selenium work in synergy to support the protective activities of immune cells. Finally, all these micronutrients, except vitamin C and iron, are essential for antibody production.

Multivitamin / multimineral combination products are directed for the prevention and therapy of respective deficiency states, since it has been proven that supplementation represents an efficient and effective mode to normalize respective under-nutrition and deficiency states and to enhance and normalize the body's immune response, thereby reducing the risk for infections. This is especially important in the elderly who have often a diminished status of several nutrients.

The composition of this product has been chosen under consideration of the immune enhancing potential of the respective selected nutrients. The amounts chosen have been determined by applying multiples of the recently evaluated RDAs of the Institute of Medicine (IOM), which is the most authoritative and in depth analysis of the currently available scientific data base.

As part of this analysis, the Institute of Medicine has also determined tolerable upper level of intakes (UL). The UL refers to the highest level of chronic daily nutrient intake by the general healthy population, at which no risk of adverse health effects is to be expected. For the preventive use of multivitamin/multimineral products, amounts of the individual nutrient of up to 5-times the recommended dietary allowance (ROA), and for therapy of already existing deficiencies amounts of up to 10-fold the respective ROA are recommended. It was decided to incorporate a higher multiple of the respective ROA for water-soluble vitamins than for fat-soluble vitamins, since water-soluble vitamins are generally not stored in the tissues and are rapidly excreted. Comparison of the concentrations of all vitamins as well as of zinc, selenium, copper, and iron in this product with the ULs values suggests that this preparation can be used chronically without any safety concern.

5.2 Pharmacokinetic properties

There is no specific study with this product but the pharmacokinetic properties of the individual components have been extensively documented.

Human health and well-being is naturally dependent on the continuous uptake and management of vitamins and trace elements and their absorption, distribution, metabolism and elimination are maintained by specific physiological mechanisms. As the tablets are completely or already dissolved in the gastro-intestinal tract a good availability of these compounds is assured. There is no specific study with this product but the pharmacokinetic properties of the individual components have been extensively documented.

5.3 Preclinical safety data

There is no specific study with this product but the preclinical safety of the individual components has been extensively documented.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Citric acid;

Sodium hydrogen carbonate;

Orange flavour (flavouring substance(s), flavouring preparation(s), sugar, maltodextrin (waxy maize) and modified starch);

Sodium carbonate;

Aspartame[1,2] (E951);

Acesulfame[1] potassium;

Beet red juice powder;

Riboflavin;

Betacarotene (betacarotene crystalline, DL-alpha-tocopherol, sodium ascorbate crystalline, medium chain triglycerides (palm oil), acacia gum, sucrose, dried glucose syrup and silicone dioxide)

Tangerine /Mandarin flavour (flavouring preparation(s), ascorbic acid, arabic gum, maize maltodextrin and modified waxy maize starch) and

Sucrose tristearate.

[1] sweetener

[2] contains a source of phenylalanine.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months

6.4 Special precautions for storage

Do not store above 25°C.

Keep the container tightly closed, in order to protect from moisture.

6.5 Nature and contents of container

15's effervescent tablets packed in a rigid polypropylene (PP) plastic tube fitted with a plastic stoper with ag desiccant in an integrated stopper. Tube(s) may be packed in a secondary packaging (folding carton), possibly with a leaflet.

6.6 Special precautions for disposal

No special requirements.

7 HOLDER OF CERTIFICATE OF REGISTRATION

Bayer (Pty) Ltd.

27 Wrench road

Isando

1600

South Africa

Co Reg. no.: 1968/011192/07

Tel: +27 11 921 5000

8 REGISTRATION NUMBER(S)

To be confirmed upon registration.

9 DATE OF FIRST AUTHORISATION/ RENEWAL OF THE AUTHORISATION

To be confirmed upon registration.

10 DATE OF REVISION OF TEXT

11 DATE OF FIRST AUTHORISATION/ RENEWAL OF THE AUTHORISATION

To be confirmed upon registration.