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

Berocca Immune Daily Defense Effervescent Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each effervescent tablet contains the following active ingredients:

Ingredient Name	Quantity
Vitamin C (Ascorbic acid)	1 000 mg
Calcium (Calcium carbonate)	250 mg
Vitamin D3 (cholecalciferol)	300 I.U.
Vitamin B6 (Pyridoxine hydrochloride)	15 mg

Contains sugar. Each tablet contains 877 mg of sucrose.

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

Berocca® Immune Daily Defense Effervescent Tablets is a combination of vitamins and calcium

designed to support the maintenance of a healthy immune system for overall health.

4.2 Posology and method of administration

Posology

For oral use.

Adult: One effervescent tablet a day dissolved in a glass of water (or as recommended by a doctor or healthcare professional).

Children 9 - 13 years old: One effervescent tablet a day dissolved in a glass of water (or as recommended by a doctor or healthcare professional).

Children 4 - 8 years old: Half an effervescent tablet a day dissolved in a glass of water (or as recommended by a doctor or healthcare professional).

Information for diabetics:

The effervescent tablets contain sugar (877 mg per tablet). It is suitable for diabetics.

4.3 Contraindications

- Hypersensitivity to any of the active substances or to any of the excipients listed in section 6.1.
- Berocca® Immune Daily Defense is not suitable for people with hemochromatosis or renal disorders. This includes patients on dialysis.
- Hypercalcaemia and/or conditions that result in hypercalcaemia such as sarcoidosis, malignancy, and primary hyperthyroidism.
- Severe hypercalciuria
- Impaired renal function
- Existing hypervitaminosis D
- Nephrolithiasis or history of nephrolithiasis
- Hyperoxaluria and/or condition resulting in hyperoxaluria
- Hemochromatosis

4.4 Special warnings and precautions for use

- Do not exceed the recommended doses. Acute or chronic overdose of > 2 g / day of vitamin C increases risk of adverse effects including formation of calcium oxalate deposits, acute tubular necrosis, and/or renal failure, especially in patients with renal disorders (see Section 4.9 Overdose section).
- Patients receiving other single vitamins or multivitamin preparations, containing vitamin D and/or calcium, any other medication or those under medical care must consult a health care professional before taking this medicinal product;
- The effervescent tablets contain sugar. This product must not be taken by patients suffering from hereditary fructose intolerance, glucose-galactose malabsorption, sucrase isomaltase insufficiency,
- The effervescent tablets contain sodium. To be taken into consideration by patients on a controlled sodium diet.
- High doses of vitamin C might interfere with diagnostic measures.
- Inform your physician when taking this product and diagnostic measures are planned or done (see Section 4.5 Interactions).
- During long-term treatment with the combination product, the serum and urinary calcium levels, and kidney function must be monitored through measurements of serum creatinine, especially in elderly patients and concomitant treatment with cardiac glycosides, calcium channel blockers, and/or thiazidediuretics.
- The combination product must be used with caution in immobilized, owing to an increased risk of hypercalcaemia.

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.
Calcium	Tetracycline antibiotics	Divalent cations, such as calcium, 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.
	Quinolone antibiotics	
	Penicillamine	
	Biphosphonates	
	Levothyroxine	
	Eltrombopag	
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®).
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.
	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.
	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.

Food / Supplement Interactions

Vitamin C

- **Iron**: Vitamin C may enhance iron absorption, especially in individuals with iron deficiency. Small increase in iron could be important in subjects with conditions such as hereditary hemochromatosis or in subjects heterozygous to this condition, as it may exacerbate iron overload

Calcium

- Oxalic acid, found in spinach and rhubarb, and phytic acid, found in whole cereals, may inhibit calcium absorption. It is not recommended to take calcium products within 2 hours of eating foods containing high oxalic acid and phytic acid concentrations
- Iron, zinc, magnesium: Calcium supplements may decrease the absorption of dietary iron, zinc, and magnesium. This might be a factor in people at high risk for deficiency of these minerals. Patient at risk for deficiency should calcium supplements at bedtime, instead of with meals, to avoid inhibiting dietary mineral absorption

Calcium and/or Vitamin D:

- Thiazide diuretics: Thiazide diuretics reduce the urinary excretion of calcium. Due to an increased risk of hypercalcemia, serum calcium should be regularly monitored during concomitant use of thiazide diuretics.
- Cardiac glycosides and Calcium Channel Blockers: Hypercalcemia increases the risk of fatal cardiac arrhythmias with cardiac glycosides such as digoxin and reduces effectiveness of calcium channel blockers such as verapamil in atrial fibrillation. It is recommended to monitor serum calcium levels, in people taking calcium and/or vitamin D and these medications, concurrently.

Vitamin D

Some medication may decrease the gastro-intestinal absorption of vitamin D. Separation of intake between these medications and vitamin D by at least 2 hours before or 4-6 hours after vitamin D should minimize this interaction.

Such medications include:

- Ion exchange resins (e.g. cholestyramine)
- Laxatives (e. g mineral oil, stimulant laxative such as senna)
- Orlistat

- Carbamazepine, phenytoin or barbiturates: Carbamazepine, phenytoin, or barbiturates increase metabolism of vitamin D to its inactive metabolite reducing the effect of vitamin D3.

Vitamin B6

- Levodopa: Pyridoxine enhances the metabolism of levodopa, reducing its anti-parkinsonism effects. However, this interaction doesn't occur when carbidopa is used concurrently with levodopa (Sinemet®)

Lab interactions

Vitamin C

- 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.
- In diabetic; 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 combination product is generally considered safe during pregnancy and lactation when the recommended dose is taken. However, since there are no sufficient controlled human studies assessing the risk of ascorbic acid treatment during pregnancy or lactation above the RDA, the product should be administered in pregnancy or lactation only when clinically indicated and recommended by the physician. The recommended dose must not be exceeded since permanent overdose might be harmful to the foetus and neonate.

Breastfeeding

During pregnancy and lactation, total daily intake from food and supplements should not exceed 2500 mg calcium and 4000 IU vitamin D.

In animals, overdoses of vitamin D during pregnancy have been shown to have teratogenic effects. There is no evidence that vitamin D at the recommended doses is teratogenic in humans.

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.

The vitamins (D, C, B6) and calcium are excreted into breast milk. This must be taken into consideration if the infant is receiving any respective supplements.

4.7 Effects on ability to drive and use machines

No effects on the ability to drive and use machines have been observed.

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

Gastrointestinal and abdominal pain, constipation, diarrhoea, nausea and vomiting may occur.

Immune system disorders

Allergic reaction, anaphylactic reaction, anaphylactic shock.

Rare hypersensitivity reactions with respective laboratory and clinical manifestations include asthma syndrome, mild to moderate reactions potentially affecting skin, respiratory tract, gastrointestinal tract, and cardiovascular system, including symptoms such as rash, urticaria, oedema, pruritus, cardio-respiratory distress, and very rarely, severe reactions, including anaphylactic shock have been reported for the single ingredients

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 Berocca® Immune Daily Defense Effervescent Tablets.

4.9 Overdose

There is no evidence that this product can lead to an overdose when used as recommended. Most, if not all reports concerning overdoses are associated with concomitant intake of high dosed single and/or multivitamin preparations.

Overdoses and chronic overdoses are reported in the medical literature for the single ingredients. Laboratory and clinical manifestations of toxicity are highly diverse and dependent on the patient's susceptibility and surrounding circumstances.

Vitamin C

Ascorbic acid overdose (> 2 g / day) may significantly elevate levels of serum and urinary oxalate levels. Increased levels of oxalate concentration have been shown to lead to calcium oxalate deposits in dialysis patients. Additionally, there are several reports which showed that large doses of vitamin C both orally and intravenously can provoke calcium oxalate deposits and calcium oxalate crystalluria in patients who have a predisposition for increased crystal aggregation, which may result in stone formation and/or, tubulointerstitial nephropathy, and acute renal failure as a result of calcium oxalate crystals

Ascorbic acid overdose (> 3 g / day in children and > 15 g / day in adults) may result in oxidative haemolysis in patients with glucose-6-phosphate dehydrogenase deficiency or disseminated intravascular coagulation.

Chronic consumption of high doses of ascorbic acid (> 500 mg / day) may exacerbate iron overload and result in tissue damage in patients with hemochromatosis.

Calcium and/or Vitamin D

Total ingestion of calcium and vitamin D in excess of 2500 mg of Calcium and 4000 IU/day of vitamin D may cause toxicity.

Patients with hypercalcaemia or conditions associated with hypercalcaemia, renal insufficiency, and/or propensity for nephrolithiasis, are susceptible to calcium and vitamin D toxicity at lower doses. Use of the product in these patient populations should be avoided.

Acute or long-term overdose of calcium and vitamin D, especially in susceptible patients, can cause hypervitaminosis D, hypercalcaemia, hypercalciuria, and hyperphosphatemia Consequences include

renal insufficiency, "Milk-alkali syndrome', vascular and soft tissue calcification including calcinosis leading to nephrolithiasis. Uncharacteristic initial symptoms, such as abrupt onset of headache, confusion, and gastrointestinal disturbances such as constipation, diarrhoea, nausea, and vomiting might be indicative for an acute overdose.

If such symptoms occur treatment must be stopped and a health care professional consulted.

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.

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

Pharmacotherapeutic group: vitamins and minerals, ATC A11JB Vitamins and minerals are essential nutrients.

Calcium metabolism and the metabolism of vitamins D_3, C, and B_6 are

intertwined particularly in bone formation.

Vitamin C

Vitamin C is an essential substance in many biochemical processes and functions physiologically as a water-soluble antioxidant by virtue of its strong reducing power. It is readily oxidized with the release of hydrogen, but the oxidation product is just as readily reduced back to ascorbic acid. Thus the vitamin participates as a hydrogen ion carrier in a redox system that is of great importance for the intermediate metabolism and cell respiration. Vitamin C has been shown to affect various components of the immune response. Vitamin C is a co-factor of many biological processes including the hydroxylation steps in the synthesis of adrenal steroid hormones, in tyrosine metabolism, and in iron metabolism and absorption. Vitamin C promotes the formation of intercellular substances (collagen, ossein and dentin) and therefore it is essential for the formation of basic collagenous matrix of the bone.

Vitamin D is of great importance for the intestinal absorption of calcium, phosphates and magnesium. It regulates the levels of these substances in body fluids and helps to maintain a normal blood calcium level. Vitamin D also contributes to the synthesis of the organic elements of the skeleton and to its calcification.

Vitamin B6 is of central importance for protein metabolism since many of the enzymes involved in the metabolism of amino acids require pyridoxine in phosphorylated form as a coenzyme. Pyridoxine regulates for example the transfer of the amino group between the various amino acids and the conversion of these acids to biogenic amines (e.g. serotonin). Vitamin B6 has been shown to play a role in immune function. Vitamin B6 participates in the transportation of calcium to the cells and the growth of intercellular substance (collagen).

Calcium is important in bone formation and plays a part in blood coagulation, muscle activity, maintenance of membrane permeability and in the conduction of nervous impulses in the neuromuscular synapses. Calcium is mainly indicated in disturbances of calcium metabolism that lead to deficiency symptoms. Calcium intake corrects a lack of calcium in the diet, especially in situations with increased requirements or decreased absorption.

5.2 Pharmacokinetic properties

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 effervescent tablets are completely dissolved in the gastro-intestinal tract, a good availability of these compounds is assured. The pharmacokinetic properties of the individual components of this product have been extensively documented.

Vitamin C

Vitamin C is readily absorbed in the upper part of the gastrointestinal tract by a sodium-dependent active transport mechanism. With higher intakes uptake occurs by means of passive diffusion. With doses up to 180 mg, 70-90% of the substance is absorbed. With intakes of 1-12 g, the proportion absorbed decreases from approximately 50% to 15%, although the absolute quantity of substance absorbed continues to increase. Vitamin C is widely distributed throughout the tissues and cellular transport of ascorbic acid is mediated by transporters that vary by cell type. Humans excrete ascorbic acid in urine, both unchanged and as metabolites. Vitamin C intakes of up to 1 g/day are mainly eliminated by renal excretion, whereas with larger intakes up to 30% of the ingested vitamin C is degraded to carbon dioxide by the intestinal flora.

Vitamin D

Vitamin D is absorbed in the small intestine and bound to specific alpha globulins and transported to the liver where it is metabolised to 25- hydroxy-cholecalciferol. A second hydroxylation to 1, 25-dehydroxy- cholecalciferol occurs in the kidney. This metabolite is responsible for the vitamin's ability to increase the absorption of calcium. Not metabolised vitamin D is stored in tissues such as fat and muscle. Vitamin D is eliminated via feces and urine.

Vitamin B6

The 3 forms of vitamin B6 (Pyridoxal, Pryidoxine and Pyridoxamine) are absorbed in the small intestine by a non-saturable, passive diffusionprocess. Vitamin B6 in a mixed diet has a bioavailability of about 75%. Absorption of vitamin B6 in the absence of food is about similar, even at higher intakes. There is significant storage of vitamin B6 in the muscle. Pyridoxal phosphate is mostly metabolized in the liver but catabolism to 4-pyridoxic acid may also occur in other tissues such as the kidney. Pyridoxic acid is irreversibly converted to 4-pyridoxic acid by an aldehyde oxidase which then is excreted in urine. About half of the daily intake of vitamin B6 is metabolized through this route and with larger intakes of pyridoxine increasing amounts of 5-pyridoxic acid are excreted.

Calcium

In the stomach, calcium carbonate releases calcium ions as a function of pH. Calcium administered as calcium carbonate is absorbed to 20 - 30% and the absorption takes place mainly in the duodenum through vitamin D-dependent, saturable, active transport. Calcium is eliminated in urine, feces and sweat. The urinary calcium excretion is a function of glomerular filtration and tubular reabsorption of calcium.

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 anhydrous,

crillet 3 (monebat 60),

orange flavour,

sodium chloride,

sodium cyclamate,

sodium hydrogen carbonate,

sucrose,

sunset yellow, and

tangerine flavour.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months

6.4 Special precautions for storage

Keep at or below 25°C.

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

6.5 Nature and contents of container

10's or 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

9 Country Estate Drive

Waterfall City, Johannesburg

2090, South Africa

Co Reg. no.: 1968/011192/07

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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.

Manufacturer:
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