1.3.1.1 PROFESSIONAL INFORMATION FOR MEDICINES FOR HUMAN USE

**SCHEDULING STATUS:**

S0

**PROPRIETARY NAME AND DOSAGE FORM:**

**BEROCCA® BOOST EFFERVESCENT TABLETS**

**COMPOSITION:**

Each effervescent tablet contains:

| **Name of Ingredient** | **Quantity** |
|---|---|
| Vitamin B1 (Thiamine hydrochloride) | 1,4 mg |
| Vitamin B2 (Riboflavin-5-Phosphate) | 1,6 mg |
| Vitamin B3 (Niacinamide) | 18 mg |
| Vitamin B5 (Calcium pantothenate) | 6 mg |
| Vitamin B6 (Pyridoxine hydrochloride) | 2 mg |
| Vitamin B7 (d-Biotin) | 0,1 mg |
| Vitamin B12 (Cyanocobalamin) | 0,001 mg |
| Folic acid | 0,2 mg |
| Vitamin C (Ascorbic Acid) | 50,00 mg |
| Calcium | 100,00 mg |
| Magnesium | 100,00 mg |
| Zinc | 9,5 mg |
| Guarana seed extract | 222,20 mg |

*Excipients:*

Acesulfame potassium, aspartame, beet root juice, citric acid, crillet 3 (Monebat 60), nature identical acerola flavour, pearlitol 160 C, sodium bicarbonate, sodium carbonate, sorbitol instant (Neosorb).

Contains sugar alcohol: Sorbitol instant (Neosorb) 367,18 mg

Contains sweeteners: Acesulfame potassium 20 mg, Aspartame 30 mg

**CATEGORY AND CLASS:**

D 34.12 Multiple substance formulation

**PHARMACOLOGICAL ACTION:**

**Pharmacodynamic properties:**

**Biotin:**

Biotin is traditionally considered to be a vitamin B substance. It is an essential coenzyme in fat metabolism and in other carboxylation reactions.

**Calcium:**

Calcium is indispensable for the growth and development of bones and teeth and for the functioning of the nervous system, processes also dependent on vitamin C and the B vitamins. Calcium deficiency is extremely common, and any supplementation of this mineral is therefore important to avoid damage to bones and teeth.

**Pantothenic acid (Vitamin B5):**

Pantothenic acid is an integral part of coenzyme A, a critical molecule in a variety of reactions such as in fatty acid metabolism. It is involved in the intermediary metabolism of carbohydrate, fats and protein leading to energy release, synthesis of fatty acids and steroids and glycogenesis.

**Ascorbic Acid (Vitamin C):**

Vitamin C is required for the synthesis of collagen, an important structural component of blood vessels, tendons, ligaments, and bone. In addition, vitamin C is required for the synthesis of carnitine, a small molecule that is essential for the transport of fat to mitochondria, for conversion to energy. Vitamin C is also a highly effective antioxidant. Even in small amounts - vitamin C can protect molecules in the body, such as proteins, lipids (fats), carbohydrates, and nucleic acids (DNA and RNA), from damage by free radicals and reactive oxygen species.

**Vitamin B1 (Thiamine):**

Thiamine acts as a coenzyme in carbohydrate metabolism. An important function of thiamine pyrophosphate (TPP) is in oxidative decarboxylation of α-keto acids, pyruvate, and α-keto-glutarate. These steps are relevant to operation of the Krebs cycle, a major source of adenosine triphosphate (ATP) generation. Thiamine pyrophosphate is also used in protein catabolism, e.g. during decarboxylation of ketoacid analogues of branched chain amino acids (valine, isoleu-cine, and leucine). Although less than 10 % of glucose is metabolized via the transketolase re-action, it is the only way the body can produce ribose for RNA synthesis. This pathway also supplies reduced NADP for various synthetic reactions, e.g. fatty acid synthesis and steroid hydroxylation.

**Vitamin B2 (Riboflavin):**

The function of riboflavin is to form the prosthetic groups of several enzyme systems (so-called flavoproteins) concerned with the oxidation reactions of tissue respiration. Thus, riboflavin is present in all cells as functioning compounds and not as stored materials.

**Nicotinamide (Niacin):**

Nicotinic acid and nicotinamide are biologically equivalent, and both are referred to as niacin (vitamin B3). The primary function of niacin, in the form of nicotinamide adenine dinucleotide (NAD) and its phosphate (NADP), is to participate in oxidation-reduction reactions in co-operation with a large number of dehydrogenases. These reactions include glycolysis, synthesis of high energy phosphate compounds, pyruvate metabolism, and pentose biosynthesis. NAD and NADP also function in lipid and protein metabolism.

**Vitamin B6 (Pyridoxine):**

Chemical compounds that have vitamin B6 activity are the alcohol (pyridoxol), the aldehyde (pyridoxal), and the amine (pyridoxamine). Vitamin B6 is rapidly converted by the liver into the metabolically active forms, pyridoxal phosphate (PLP) and pyridoxamine phosphate. These compounds are distributed throughout animal tissues but none are stored.

The function of vitamin B6, primarily as PLP or rarely as pyridoxamine phosphate is to act as a cofactor for an exceptionally large number of enzymes involved in synthesis or catabolism of amino acids.

LP is also required for the synthesis of δ-aminolevulinic acid, a precursor of heme. A large percentage of body vitamin B6 is found in phosphorylase, the enzyme which converts glycogen to glucose-1-phosphate.

Approximately one-half the vitamin B6 found in the body can be accounted for in the phosphorylase of skeletal muscle.

**Vitamin B12 (Cyanocobalamin):**

Vitamin B12 is required for the function of the folate-dependent enzyme, methionine synthase. This enzyme is required for the synthesis of the amino acid methionine from homocysteine. Methionine in turn is required for the synthesis of S-adenosylmethionine, a methyl group do-nor used in many biological methylation reactions, including the methylation of a number of sites within DNA and RNA.

**Folic Acid:**

Folate coenzymes act as acceptors and donors of one-carbon units in a variety of reactions critical to the metabolism of nucleic acids and amino acids. Deficiency of the vitamin leads to impaired cell division and to alterations in protein synthesis, effects most noticeable in rapidly growing tissues.

**Magnesium:**

Magnesium is an essential body electrolyte. It is the second most important in intracellular fluid, is a co-factor in numerous enzyme systems, is involved in phosphate transfer, muscle contractility, neuronal transmission, and is believed to be essential for the structural stabilization of nucleic acids in large therapeutic dosages.

**Zinc:**

Zinc is an essential nutrient and plays an important role in maintenance of human health. It is important in cellular growth and differentiation with profound effects on the immune system, in collagen synthesis, and in antioxidant defense. Zinc has antioxidant capacity and contributes to the protection of cells from the damaging effects of reactive oxygen radicals and reactive nitrogen species produced during processes such as immune activation. The catalytic function of zinc is required for biological activity of more than 300 enzymes and zinc enzymes are found in all six International Union of Biochemistry (IUB) classes. In addition to its role in many enzymes, zinc helps to stabilize the structures of membranes, RNA, DNA, and ribosomes.

**Guarana:**

Guarana, an extract made from the berries of the Amazonian plant Paullinia cupana, that has been shown to improve measures of attention and secondary memory, and to increase alertness and contentment ratings. Its

stimulant properties are usually attributed to its caffeine content (2,5–5% of dry weight), which is known to modify cognitive function and mood state and to enhance exercise performance. Guarana also contains caffeine, methylxanthines, theophylline and theobromine, as well as saponins and tannins.

**Pharmacokinetic properties:**

**Biotin:**

**Absorption:**

Biotin is absorbed in the intestine by a saturable, sodium dependent transporter. The transport of biotin was examined in different areas of the human small intestine and was found to be saturable in the presence of a sodium gradient but was linear in the presence of a choline gradient.

Transport by the sodium-dependent process was noted to be higher in the duodenum than the jejunum, which was in turn higher than that in the ileum, and it was concluded that the proximal part of the human small intestine was the site of maximum transport of biotin.

**Distribution:**

For the evaluation of biotin nutritional status in humans, the circulating levels of the vitamin in whole blood, plasma, or serum and the urinary biotin excretion are employed. These levels are assessed mainly by microbiological methods and the great variation in the reported values can be due, in both urine and blood, to the analytical method. Reported values for circulating blood levels seem to range from (mean±SD) 934±385 to 4781±2174 pmol biotin /liter. A circulating level in blood, plasma, or serum of around1500 pmol/liter seems to indicate an adequate supply for biotin in humans.

Biotin serves as a prosthetic group in a number of enzymes in which the biotin moiety functions as a carboxyl carrier, i.e. enzymes that transport carboxyl units and fix carbon dioxide in animal tissue. The biotin-dependent enzymes can be divided into carboxylases (e.g. pyruvate carboxylase, acetyl-CoA carboxylase, etc.), transcarboxylase (methylmalonyl-CoA carboxyl-transferase), and decarboxylases (methylmalonyl-CoA decarboxylase, oxaloacetate decarboxylase). Tissues containing biotin-dependent enzymes include liver, kidney, brain and heart. The activities of the biotin-dependent enzymes in the various tissues are rapidly restored on administration of the vitamin to deficient animals. The rate of restoration of activities differs for the different tissues; it is fastest in kidney and brain and slower in liver and heart. This might be indicative of differences in the availability of the vitamin to the various tissues or the rates at which the holoenzymes are synthesized.

**Metabolism:**

Any investigation into the metabolism of biotin in animals and humans is complicated by the fact that biotin-

producing microorganisms exist in their intestinal tract distal to the cecum. There are indications that in plasma part of the circulating biotin is bound to proteins.Biotinidase was found to be the only protein in human serum that exchanges [3H](+)-biotin, and thus biotinidase could be the major carrier of biotin in plasma, and as such function in biotin transport. Very little is known about biotin catabolism. The mammal does not seem able to degrade the ring system of biotin. In the urine of healthy humans small amounts of biotin metabolites have also been detected, none of which were biotinsulfoxide or biotinsulfone. The catabolism of biotin-containing holocarboxylases can lead to biocytin, from which biotin can be liberated by biotinidase, leading to a endogenous recycling of biotin.

**Excretion:**

Quite large day-to-day variations in fecal biotin excretion have been found, but excretion in feces is always greater than in urine. From the available data, a biotin level in urine of approximately 160 nmol per 24 hour or 70 nmol/liter seems to indicate an adequate supply of biotin for humans.

**Calcium:**

**Absorption:**

The amount of calcium absorbed depends on its interaction with other dietary constituents, and on physiological factors such as calcium-regulating hormones and stage of the life span. In general, the absorption of calcium supplements is better if they are taken with a meal. This may be because the.meal stimulates gastric secretion and delays emptying, so that the calcium sources are better dispersed and dissolved.

There are two routes of calcium absorption in the intestine. One is an active, saturable, transcellular process that occurs mainly in the duodenum and proximal jejunum and is regulated by vitamin D. Ileal absorption may also be affected by vitamin D status. The other pathway of calcium absorption is a passive, nonsaturable, paracellular route that is independent of vitamin D regulation and occurs throughout the small intestine. The amount of calcium absorbed by this way depends primarily on its quantity and availability in the diet. Intakes above as little as 3 mmol (120 mg) in a meal will probably be absorbed passively by the small intestine. Most calcium absorption occurs in the ileum, where food remains for the longest time.

**Distribution:**

Because more than 99 % of the body’s calcium is in bone, the skeleton is the major storage site for the maintenance of extracellular fluid (ECF) calcium. In the short term, negative calcium balance involves a harmless mobilization of bone calcium. In the longer term, the chronic removal of skeletal calcium has adverse effects on bone strength. The level of ionized calcium in plasma is controlled by an integrated response of the calcium-regulating hormones that affect calcium transport in the intestine, bone and kidney. Of these the most important

are parathyroid hormone (PTH), calcitonin and vitamin D. Serum calcium by inhibiting bone resorption and agents that have a resorptive effect on bone. These include PTH, vitamin D metabolites and vitamin A. The most active vitamin D metabolite is 1,25(OH)2D. In calcium deficiency more 1,25(OH)2D is produced, causing enhanced intestinal absorption and renal absorption of calcium, and increased bone formation as well as resorption. The 1 % extraskeletal calcium is found in extracellular fluids, intracellular structures, and cell membranes.

**Metabolism:**

Calcium has a structural role in bone and teeth. Bone calcium is relied upon to maintain ECF calcium concentrations, which in turn are necessary for normal neuromuscular and other functions. The extracellular calcium plays an essential role in such vital functions as nerve conductance, muscle contraction, blood clotting, and membrane permeability.

**Excretion:**

Calcium is excreted in approximately equal amounts in urine and endogenous secretions. Calcium loss from the skin is only 0,4 mmol per day (15 mg per day), although this will increase substantially with increased sweating.

**Pantothenic acid (Vitamin B5):**

**Absorption:**

Pantothenic acid is thought to be absorbed principally in the jejunum by passive diffusion, although animal data suggest that low amounts may be absorbed by an active process. Absorption seems to decrease when ingestion approaches levels of ten-times the recommended amounts in supplements. From the blood, uptake by heart, muscle and liver occurs by active transport, whereas uptake in the central nervous system, adipose tissue, and kidneys is by facilitated diffusion.

**Distribution:**

High concentrations (2-4 mg per 100 g) of pantothenic acid are found in liver, kidney, brain, and heart. Examination of the organs of rats revealed that, next to the liver, the adrenal gland contained the highest concentration of coenzyme A, suggesting a close relationship between pantothenic acid level and adrenal cortex function. Pantothenic acid is found in whole blood, plasma, serum, and red blood cells. The majority of the vitamin exists in the red blood cells as coenzyme A, and the serum reportedly contains no coenzyme A but does contain free pantothenic acid. Levels of pantothenic acid in the red blood cells are higher than levels of pantothenic acid in the plasma, and also red blood cells are more affected by dietary pantothenic acid. Total pantothenic acid levels below 100 µg/dl may be indicative of low levels of pantothenic acid in the diet. Total pantothenic acid content of whole blood for men of different age groups ranged from 94,0 to 117,4 µg/dl, and for

women from 87,1 to 109,6 µg/dl.

**Metabolism:**

Pantothenic acid plays its primary physiological roles as a component of the coenzyme A molecule and within the 4'-phosphopantetheine moiety of the acyl carrier protein (ACP) of fatty acid synthetase, which serves in acyl-group activation and transfer reactions. These reactions are important in the release of energy from carbohydrates; in gluconeogenesis; in the synthesis and degradation of fatty acids; in the synthesis of such vital compounds as sterols. and steroid hormones, porphyrins, and acteylcholine; and in acylation reactions in general. Pantothenic acid deficiency notably affects the adrenal cortex, the nervous system, skin, and hair.

**Excretion:**

Free pantothenic acid is excreted in the urine

**Ascorbic Acid (Vitamin C):**

**Absorption:**

Ascorbic acid is widely absorbed from the gastrointestinal tract. Ascorbic acid is absorbed primarily in the upper part of the small intestine via sodium-dependent active transport. When ascorbic acid is present in high concentrations, uptake occurs by means of passive diffusion. After oral administration of doses up to about 180 mg, 70-90 % of the substance is absorbed. With doses of 1-12 g, the proportion of ascorbic acid absorbed falls from approximately 50 % to about 15 %, though the absolute quantity of substance taken up continues to increase.

**Distribution:**

Plasma protein binding of ascorbic acid is approximately 24 %. Serum concentrations are normally 10 mg/l (60 µmol/l). Concentrations below 6 mg/l (35 µmol/l) indicate that the intake of vitamin C is not always adequate, and concentrations below 4 mg/l (20 µmol/l) indicate that the intake is actually inadequate. In clinically manifest scurvy, serum concentrations are below

2 mg/l (10 µmol/l).

**Metabolism:**

Ascorbic acid is metabolized partly via dehydroascorbic acid to oxalic acid. When ingested in excessive quantities, however, ascorbic acid is largely excreted in unchanged form in the urine and faces. Ascorbic-acid-2-sulphate also appears as a metabolite in the urine.

**Excretion:**

The physiological body pool is about 1500 mg. The elimination half-life of ascorbic acid depends on the route of

administration, the quantity administered and the rate of absorption.

**Vitamin B1 (Thiamine):**

**Absorption:**

Thiamine is rapidly absorbed, largely in the proximal small intestine. There are two transport mechanisms, one by an active process at < 2 µM, one by passive diffusion at > 2 µM.

**Distribution:**

Average total amount of vitamin B1 in adult humans is approximately 30 mg. High concentrations are found in skeletal muscle, heart, liver, kidney and brain. In the spinal cord and the brain, the thiamine level is about double that of peripheral nerves. The whole-blood thiamine varies from 5 to 12 µg per 100 ml, 90 % of which is in the red cells and leukocytes. Leukocytes have a 10-fold higher concentration than red cells. Thiamine has a relatively high turnover rate in the body and is not stored in large amounts for any period of time in any tissue. Hence, a continuous supply is necessary. Relatively short periods of time with inadequate intake can lead to biochemical, followed by clinical, signs of deficiency. When the intake is about 60 µg per 100 g body weight (or 42 mg per 70 kg) and the total body thiamin reaches 2 µg/g (or 140 mg per 70 kg), a plateau is reached in most tissues.

**Metabolism:**

Oral (or parenteral) thiamine is quickly converted to the diphosphate and to a smaller extent the triphosphate esters in the tissues. All thiamine in excess of tissue needs and binding and storage capacity is rapidly excreted in the urine. Stimulation of nerves causes the release of thiamine or the monophosphate with a concomitant decrease in the tri- and diphosphates.

**Excretion:**

Vitamin B1 is excreted in the urine. In addition to free vitamin B1 and a small amount of thiamin diphosphate, thiochrome, and thiamin disulfide, about 20 or more metabolites of vitamin B1 have been reported in the urine of rats and humans but only six have really been identified. The relative proportion of metabolites to vitamin B1 excreted increases with decreasing vitamin B1 intake.

**Vitamin B2 (Riboflavin):**

**Absorption:**

Riboflavin is readily absorbed, largely in the proximal small intestine.

Absorption involves an active, saturable transport system. Free riboflavin is phosphorylated to riboflavin 5'phosphate (or FMN: flavin mononucleotide). FMN then enters the portal system, where it is bound to plasma

albumin and transported to the liver, where it is converted to FAD (flavin adenine dinucleotide).

**Distribution:**

Riboflavin and FMN are converted to FAD in the tissues where binding to specific flavoproteins occurs. The liver, the major site of storage, contains about one-third of the total body flavins. The liver, kidney, and heart have the richest concentrations of this vitamin, and 70-90 % is in the form of FAD. Free riboflavin constitutes less than 5 % of the stored flavins. In the human brain, the riboflavin content is higher in the basal ganglia and temporal cortex than

in the frontal cortex.

**Metabolism:**

In tissues, FAD can be hydrolyzed to FMN and free riboflavin by phosphates and nucleotidases. Flavins bound to protein are resistant to hydrolysis, and this probably accounts for the fact that significant stores of flavin remain in the livers of animals that die of riboflavin deficiency.

**Excretion:**

Riboflavin is excreted primarily in the urine, with bile and sweat as minor routes of excretion. Studies of turnover rate of riboflavin in normal rat tissue have shown that the half-life is about 16 days. Riboflavin is excreted primarily unchanged, since no decomposition product has been found in either tissues or urine. The urinary excretion of riboflavin is about 200 µg per 24 hour in normal adults. In riboflavin deficiency this decreases to 40-70 µg per 24 hour.

Nearly all of a large oral dose of riboflavin is excreted in the urine of normal adults. The peak of excretion occurs within 2 hours. This becomes visible in individuals who take a dose of riboflavin, either in a vitamin pill or in enriched foods in following way. After about 2 hour the color of urine will change from straw color to an orange-yellow hue.

**Nicotinamide (Niacin):**

**Absorption:**

Niacin is the generic term that includes both nicotinic acid and nicotinamide.

Both vitamins are absorbed by facilitated diffusion at low concentrations and by passive diffusion at higher concentrations, and both appear in blood plasma. Even large doses (24,6 mmol (3 g) or more) of niacin are efficiently absorbed from the intestine.

**Distribution:**

Niacin is rapidly removed from blood plasma by the tissues, particularly the liver and red cells; in the post

absorption state only small amounts remain in plasma. Once niacin enters the cell it is converted to its coenzyme forms, nicotinamide adenine dinucleotide (NAD) and NAD phosphate (NADP). In addition to NAD bound to enzymes, NAD not attached to an apoenzyme may also be present. This free NAD is sometimes designated as 'storage' NAD. In the rat, high concentrations of NAD are found in heart, liver, kidney, and muscle tissue.

**Metabolism:**

In the liver, any excess of free niacin that accumulates is methylated to N1-methyl-nicotinamide (NMN) by N-methyl transferase. The hydrolysis of hepatic NAD stores to nicotinamide and adenosine diphosphate ribose (ADPR) is of particular importance in niacin metabolism because it allows the release of nicotinamide for transport to and absorption by tissues needing niacin. The hydrolysis of NAD (and NADP) in the liver and other tissues is catalyzed by two classes of enzymes, the NAD glycohydrolasas and the poly (ADPR) polymerases. The activity of these enzymes appears to account in large measure for the rapid turnover of the pyridine nucleotides. Some bound forms of NAD, however, are relatively immune to glycohydrolase action. The NAD of glyceraldehyde 3-phosphate dehydrogenase is one example thus ensuring that the glycolysis pathway will be spared to some extent in niacin deficiency states.

**Excretion:**

NMN is the major niacin metabolite excreted in the urine. Other metabolites found in urine include the oxidized derivatives of NMN, 2- and 4-methyl pyridone, and nicotinuric acid, the conjugate of nicotinic acid and glycine. The oxide and hydroxyl forms of niacin are also excreted in small amounts.

**Vitamin B6 (Pyridoxine):**

**Absorption:**

Vitamin B6 is readily absorbed via the gastrointestinal tract after oral doses.

Vitamin B6 comprises three chemically, metabolically, and functionally related forms: the alcohol pyridoxine (pyridoxol, PN), the aldehyde pyridoxal (PL), and the amine pyridoxamine (PM). The various dietary forms of vitamin B6 are absorbed by intestinal mucosal cells through a nonsaturable process.

**Distribution:**

The B6 forms are converted in the liver, erythrocytes and other tissues to pyridoxal phosphate (PLP) and pyridoxamine phosphate (PMP). These compounds are distributed throughout animal tissues but none are stored. A large percentage of body vitamin B6 is found in phosphorylase, the enzyme that converts glycogen to glucose-1-phosphate. Approximately half the vitamin B6 found in the body can be accounted for in the phosphorylase of skeletal muscle. PLP is present in the plasma as a PLP-albumin complex and in erythrocytes in

association with hemoglobin. The PL concentration in the erythrocyte is up to four to five times greater than that in plasma

**Metabolism:**

PLP and PMP act primarily as coenzymes in transamination reactions; primarily PLP acts as a cofactor for an exceptionally large number of enzymes involved in the synthesis or catabolism of aminoacids. PLP also participates in decarboxylation and racemization of A-amino acids, in other metabolic transformations of amino acids, and in the metabolism of lipids and nucleic acids. In addition, it is the essential coenzyme for glycogen phosphorylase. Pyridoxal phosphate is also required for the synthesis of δ-aminolevulinic acid, a precursor of heme.

**Excretion:**

The phosphoric acid esters of the active forms of vitamin B6 undergo hydrolysis before release from the cells. PL can be further oxidized to pyridoxic acid and other inactive oxidation products, which are then excreted in the urine.

**Folic Acid:**

**Absorption:**

Folic acid is rapidly absorbed from the gastrointestinal tract, mainly from the duodenum and jejunum and it is stated that folates have about half the bioavailability of crystalline folic acid.

**Distribution:**

The total content of folate in the liver has been estimated from biopsies and autopsy material to 6-14 mg, and total body folate to approximately 22 mg (range 15-30 mg). Reserves are relatively low, also indicated by an overall half-life of about 100 days. Approximately two-thirds of folate in the plasma is protein bound, mainly as 5-methyl THF. The normal plasma concentration of folate is about 7-17 ng/mL, mainly represented by 5-methyl THF monoglutamate. After uptake of folate by the cells, mediated by a specific membrane bound protein, folate is stored in the cells after demethylation as the polyglutamate.

**Metabolism:**

The results of studies that were carried out indicate that further that about 1 % of the total folate body pool/day is catabolized or excreted. Long nutritional intervention is required to achieve a new steady-state.

**Excretion:**

Urinary excretion of intact folate, which is not associated to protein, is minimal, also due to the efficient re-absorption in the proximal tubuli (10-20 % of absorbed folate). Fecal folate excretion occurs but it is difficult to

estimate due to microbial synthesis in the intestine. The main route of folate catabolism is cleavage resulting in pteridines and para-amino benzoylglutamate which is excreted as the N-acetyl compound in the urine.

**Vitamin B12 (Cyanocobalamin):**

**Absorption:**

Cobalamins can be absorbed by two different mechanisms.

- An active mechanism (intrinsic factor mediated). The active mechanism is mediated by an intrinsic factor, a glycoprotein secreted by the parietal cells of the gastric mucosa. It is of primary importance in the absorption of physiological doses of cobalamin (approximately 1-5 µg).
- A diffusion-type mechanism (non-intrinsic factor mediated). The diffusion-type mechanism is operative when the amount of vitamin is large, usually in excess of the amount available from the diet. About 1 % of an oral dose of 100 µg and more of cobalamin is absorbed in pernicious anemia patients.

**Distribution:**

In plasma and tissue, the predominant forms are methylcobalamin, adenosyl cobalamin, and hydroxycobalamin. Methylcobalamin constitutes 60-80 % of the total plasma cobalamin. In normal human subjects, cobalamins are found principally in the liver, where the average amount is 1,5 mg. The kidneys, heart, spleen, and brain each contain about 20-30 µg. Mean values for the total body content calculated for human adults range from 2 to 5 mg. The pituitary gland has the greatest concentration per gram of tissue of any organ. Adenosylcobalamin is the major cobalamin in all the cellular tissues, constituting about 60-70 % in the liver and about 50 % in the other organs.

**Metabolism:**

In crossing the intestinal mucosa, vitamin B12 is transferred to the plasma transport protein transcobalamin II, which delivers the vitamin to cells. The specific biochemical reactions in which the cobamide coenzymes participate are of two types: (1) those that contain 5'-deoxyadenosine linked covalently to the cobalt atom (adenosylcobalamin), and (2) those that have a methyl group attached to the central cobalt atom (methylcobalamin). The coenzyme methylcobalamin catalyzes a transmethylation from a folic acid cofactor to homocysteine to form methionine. This reaction releases the unmethylated folate cofactor for other single carbon transfer reactions important to nucleic acid synthesis. The other cobalamin coenzyme, deoxyadenosylcobalamin, catalyzes the conversion of methylmalonyl-coenzyme A to succinyl-coenzyme A, a reaction in the pathway for the degradation of certain amino acids and odd-chain fatty acids.

**Excretion:**

Excretion occurs via urinary, biliary, and fecal routes. These are the main excretion pathways. Only the unbound plasma cobalamin is available for urinary excretion and, therefore, urinary excretion by glomerular filtration of free cobalamin is minimal, varying up to 0,25 µg per day. Approximately 0,5-5 µg of cobalamin is secreted into the alimentary tract per day, mainly in the bile, of which at least 65-75 % is reabsorbed in the ileum by means of the intrinsic factor mechanism.

**Magnesium:**

**Absorption:**

Absorption of magnesium as a function of intake appears curvilinear. The curved portion is compatible with a saturable process (facilitated diffusion or active absorption) and the linear function reflects passive diffusion. Passive diffusion has been estimated to contribute around 7-10 %. Intestinal perfusion techniques in human subjects indicate magnesium to be absorbed by both jejunum and ileum with absorption being fully saturable in the ileum but not the jejunum.

**Distribution:**

More than half the total body magnesium is found in bone (60-65 %) with almost all the rest in soft tissue: muscle 27 %, other cells 6-7 %, extracellular < 1 %. The greater proportion of intracellular magnesium exists in bound form, e.g. in muscle mainly bound to adenosine triphosphate (ATP), phosphocreatine and myosin. Average plasma magnesium concentration is about 0,85 mM (range 0,65 to 1,0 mM) and is maintained remarkably constant in healthy individuals by poorly understood homeostatic controls, which do not appear to be regulated by hormonal mechanism.

**Metabolism:**

There a number of biochemical and physiological processes require or are modulated by magnesium. As the Mg-ATP2- complex, magnesium is important for all biosynthetic processes, for glycolysis, formation of cyclic-AMP (adenosine monophosphate), energy-dependent membrane transport, and transmission of the genetic code.
More than 300 enzymes are known to be activated by magnesium.

**Excretion:**

Magnesium is retained either for tissue growth (including bone) or as turnover replacement; the remainder is excreted in the urine. Plasma magnesium levels are believed to be regulated primarily by the kidney.
Approximately 70 % of plasma protein is not bound to protein and is therefore filterable.
About 30 % of filtered magnesium is reabsorbed in the proximal tubule and another 65 % is reabsorbed in the loop of Henle, the site at which major adjustments in response to plasma concentrations appear to take place.

**Zinc:**

**Absorption:**

The vast majority of ingested zinc is absorbed by the small intestine through a transcellular process with the jejunum being the site with the greatest transport rate. Only small amounts are absorbed in the stomach and large intestine. Absorption kinetics appear to be saturable, and there is an increase in transport velocity with zinc depletion. Transfer from the intestine is via the portal system with most newly absorbed zinc bound to albumin.

**Distribution:**

The total body zinc content is controlled in part by regulating the efficiency of intestinal absorption and the excretion from endogenous zinc pools. As intraluminal concentrations of zinc rise, the fractional absorption of zinc decreases, but the actual amount of zinc absorbed rises linearly. Endogenous faucal zinc losses can be increased several fold to maintain zinc homeostasis with high intake of zinc.

**Metabolism:**

A two-component model best explains the elimination of absorbed zinc from the body. In humans, the initial rapid phase has a half-life of 12,5 days, and the slower turnover phase has a half-life value of about 300 days. The initial rapid half-life primarily represents liver uptake of circulating zinc and its release. The slower turnover rate reflects differing rates of zinc turnover in various tissues other than the liver. Zinc uptake by the central nervous system and bones is relatively slow. The pancreas, liver, kidney, and spleen have the most rapid rates of accumulation and turnover; uptake and exchange of zinc in the red blood cells and muscle are slower than in the viscera.

**Excretion:**

The major route for endogenous zinc excretion is into the gastrointestinal tract with ultimate loss in the faeces. Secretion of endogenous zinc into the small intestine is believed to be primarily via pancreatic exocrine secretions and possibly the intestinal mucosa. A percentage of this endogenous zinc is reabsorbed, which is essential to maintain hemostasis. When tracer doses of zinc are given either orally or intravenously, only about 2 % to 10 % is recovered in the urine; the remainder is lost in the faeces.

**Guarana**

Caffeine is the major active component of Guarana

**Absorption**:

Caffeine is absorbed readily after oral administration and is widely distributed throughout the body.

**Distribution:**

Caffeine passes readily into the central nervous system and into the saliva; low concentrations are also present in breast milk. Caffeine crosses the placenta.

**Metabolism:**

Caffeine is metabolised almost completely in the liver via oxidation, demethylation and acetylation. The metabolism of caffeine is dose-dependent with clearance decreasing as the dose is increased.

**Excretion:**

Caffeine is excreted in urine as 1-methyluric acid, 1-methylxanthine, 7-methylxantrhine, 1,7-dimethylxanthine (paraxanthine), 5-acetylamino-6-formylamino-3-methyluracil (AFMU), and other metabolites with only about 1 % unchanged.

The plasma half-life of caffeine of caffeine is decreased by smoking and by exercise, and is increased by liver disease such as cirrhosis and viral hepatitis, and in pregnancy.

**INDICATIONS:**

The combination of vitamin B-complex, vitamin C, minerals and guarana works in synergy to increase physical energy while decreasing tiredness, and provides you with the essential micro-nutrients for sustained mental performance.

**CONTRAINDICATIONS:**

- Hypersensitivity to the active ingredients and to any of the inactive ingredients of BEROCCA® BOOST EFFERVESCENT TABLETS (see **COMPOSITION**).
- Hypercalcaemia
- Severe hypercalciuria
- Severe renal insufficiency (GFR < 30ml/min) including individuals on dialysis
- Hyperoxaluria
- Nephrolithiasis or history of nephrolithiasis

**WARNINGS AND SPECIAL PRECAUTIONS:**

Do not exceed the labeled dose. Acute and chronic overdose increases the risk of side effects.

Individuals receiving other single vitamins or multivitamin preparations, any other medication, placed on a restricted diet, or those under medical care should consult a healthcare professional before use of the product.

Intake of the product should be separated from other medications by 4 hours unless otherwise specified.

**BEROCCA® BOOST EFFERVESCENT TABLETS** may interfere with laboratory tests resulting in false readings. Therefore patients should inform doctors or healthcare professionals when taking this product and laboratory tests are planned.

Vitamin C may interfere with testing kits and meters that measure glucose levels resulting in false readings.

Vitamin C increases iron absorption. Individuals with hemochromatosis should use precaution with use of the product and avoid intake of vitamin C > 500 mg/day.

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 hemolytic anemia.

This product is not formulated for the treatment of vitamin B12 deficiency due to atrophic gastritis, disorder of the ileum or pancreas, and gastro-intestinal malabsorption of vitamin B12 or intrinsic factor deficiency.

Individuals with phenylketonuria should avoid products that contain aspartame as it is a source of phenylalanine, therefore this product should be avoided.

These effervescent tablets contain sodium. This should be taken into consideration by individuals on a controlled sodium diet.

The levels of calcium and magnesium in the product contribute to the recommended daily intake, but the intake of the product at the labeled dose as the only source of calcium and magnesium cannot be regarded as sufficient for the treatment of calcium and/or magnesium deficiencies, or for the therapeutic functions of these elements apart from their role as cofactors in the activation and action of B vitamins.

Patients with the rare hereditary condition of sorbitol intolerance should not take **BEROCCA® BOOST EFFERVESCENT TABLETS**

**Effects on the ability to drive and use machiner**y:

**BEROCCA® BOOST EFFERVESCENT TABLETS** have no or negligible influence on the ability to drive and use machines.

**Excipients:**

**BEROCCA® BOOST EFFERVESCENT TABLETS** contains sorbitol. Patients with the rare hereditary condition of sorbitol intolerance should not take **BEROCCA® BOOST EFFERVESCENT TABLETS**

Consumption of greater than 10 g of sorbitol may cause a laxative effect hence the recommended does should not be exceeded.

.

**BEROCCA® BOOST EFFERVESCENT TABLETS** contains aspartame which is a source of phenylalanine which may be harmful to people with phenylketonuria.

**INTERACTIONS:**

Potential interactions are reported in the literature for the single ingredients.

| **Active Ingredient** | **Medicine** | **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. |
| | Warfarin | High dose vitamin C may interfere with the effectiveness of warfarin. |
| Vitamin $B_6$ | Levodopa | Pyridoxine enhances the metabolism of levodopa, reducing its antiparkinsonism effects. However, this interaction does not occur when carbidopa is in combination with levodopa. |
| Vitamin $B_{12}$ | Choramphenicol | Chloramphenicol may delay or interrupt the reticulocyte response to vitamin $B_{12}$. Therefore, blood counts need to be closely monitored if this combination can't be avoided. |
| 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. |
| Calcium | 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. |
| Magnesium, Zinc | Potassium-Sparing Diuretics | Potassium-sparing diuretics also have magnesium-sparing and/or zinc-sparing properties. Increased magnesium and/or |

| | | |
|---|---|---|
| | | zinc levels could result with concomitant use of potassium-sparing diuretics and supplementation. |
| Calcium, Magnesium, Zinc | Tetracycline antibiotics | Polyvalent cations, such as calcium, magnesium, and/or zinc, form complexes with certain substances resulting in decreased absorption of both substances. Separate intake of the product either 2 hours before or 4 hours after other medication, unless otherwise specified, will minimize risk for this interaction. |
| | Quinolone antibiotics | |
| | Penicillamine | |
| | Biphosphonates | |
| | Levothyroxine | |
| | Methyldopa | |
| | Mycophenolate mofetil | |
| | Eltrombopag | |

**HUMAN REPRODUCTION:**

**Pregnancy:**

The product is generally considered safe during pregnancy or lactation when taken as labeled. However, 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 when clinically indicated and recommended by a doctor or healthcare professional.

The labeled dose should not be exceeded since chronic overdose might be harmful to the fetus and neonate.

Allowance should be made for intake of the vitamins and minerals from all other sources.

Caffeine crosses the placenta.

**Lactation:**

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

**DOSAGE AND DIRECTIONS FOR USE:**

Adults and adolescents:

1 effervescent tablet daily dissolved in a glass of water (200 ml).

The recommended daily dose of one tablet per day must not be exceeded unless under supervision of a doctor, pharmacist or other healthcare professionals.

**BEROCCA® BOOST EFFERVESCENT TABLETS** is not recommended for children below 12 years.

**SIDE EFFECTS:**

**BEROCCA® BOOST EFFERVESCENT TABLETS** may have side effects.

**Immune system disorders**

Frequency unknown: Hypersensitivity reactions or anaphylaxis. Symptoms may include difficulty breathing or swallowing, angioedema, itchy throat, skin reddening, rash.

**Gastrointestinal disorders:**

Rare: abdominal discomfort, constipation, nausea, diarrhoea, vomiting

**Renal and urinary disorders**

*Rare:* A slight orange-yellow discolouration of urine may be noticed.

This effect is harmless and is due to the vitamin B2 contained in the preparation.

**KNOWN SYMPTOMS OF OVER DOSAGE AND PARTICULARS OF ITS TREATMENT**

There is no evidence that this product can lead to an overdose when used as recommended. General manifestation of overdose may include confusion and gastrointestinal disturbances such as constipation, diarrhea, nausea, and vomiting.

If such symptoms occur, the product should be stopped and a healthcare professional should be consulted for treatment of clinical manifestations.

**Vitamin C**

Acute or chronic overdose of vitamin C (> 2 g / day in adults) may significantly elevates 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.

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

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 hemolysis or disseminated intravascular coagulation.

**Vitamin B6**

Intake above UL (> 60 mg in adolescents 12 of age and 100 mg/day in adults) increases risk of 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.

**Zinc**

Zinc overdose (> 40 mg / day in adults) can cause diarrhea, irritation, and corrosion of the gastrointestinal (GI) tract, acute renal tubular necrosis, interstitial nephritis, copper deficiency, sideroblastic anemia and myeloneuropathies.

**IDENTIFICATION:**

A speckled purple, smooth, cylindrical, bevelled edge tablet.

**PRESENTATION:**

**BEROCCA® BOOST EFFERVESCENT TABLETS** are packed in polypropylene tubes including a desiccant and a white cap.

The tubes are packed into a carton in pack sizes of 10’s and 15’s tablets.

**STORAGE INSTRUCTIONS:**

Store in the original container at or below 25 °C.

Store in a cool dry place.

Keep the container tightly closed.

KEEP OUT OF REACH OF CHILDREN.

**REGISTRATION NUMBER:**

To be allocated.

**NAME AND BUSINESS ADDRESS OF THE HOLDER OF CERTIFCATE OF REGISTRATION:**

Bayer (Pty) Ltd.

27 Wrench Road

Isando, 1600

South Africa

Co Reg. No: 1968/011192/07

Tel: +27 11 921 5000

**DATE OF PUBLICATION OF THE PROFESSIONAL INFORMATION:**

**Date of registration**: To be allocated.

**Date of the most recent amendment to the professional information as approved by the Authority:** To be allocated.