SELECT THE REQUIRED INFORMATION

PROFESSIONAL INFORMATION

PATIENT INFORMATION LEAFLET

COMPLEMENTARY MEDICINE: HEALTH SUPPLEMENT
This unregistered medicine has not been evaluated by the SAHPRA for its quality, safety or intended use.

SCHEDULING STATUS: S0

1. NAME OF THE MEDICINE

Berocca Mind Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Berocca Mind Tablets is a combination of *Salvia lavandulaefolia*, water-soluble vitamins, and select minerals
Each film-coated tablet contains the following active ingredients:

Ingredient Name	Quantity
Vitamin B1 (thiamine mononitrate)	1,4 mg
Vitamin B2 (riboflavin)	1,6 mg
Vitamin B3 (nicotinamide)	18 mg
Vitamin B5 (calcium-D-pantothenate)	6 mg
Vitamin B6 (pyridoxine hydrochloride)	2 mg
Folic acid (pteroylmonoglutamic acid)	200 µg
Vitamin B12 (cyanocobalamin)	2,5 µg
Biotin (D-biotin)	150 µg
Vitamin C (ascorbic acid)	60 mg
Magnesium (magnesium oxide)	135 mg
Iron (ferrous fumarate)	12 mg
Zinc (zinc citrate)	4,6 mg
Salvia Lavandulifolia oil (providing 25 µl Sage essential oil)	147 mg

Sugar free.
For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated Tablet.
Light green, oblong and biconvex film coated tablet.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Helps maintain optimal mental well-being and memory
- Contributes to normal cognitive function
- Contributes to normal psychological function
- Contributes to normal mental performance
- Contributes to normal functioning of the nervous system
- Contributes to normal muscle function

• Contributes to a reduction of tiredness and fatigue
• Contributes to normal energy-yielding metabolism

4.2. Posology and method of administration

Posology

For oral use.
One tablet per day in people 18 years of age or older.

4.3. Contraindications

- Hypersensitivity to any of the active substances or to any of the excipients listed in section 6.1.
- Berocca Mind Tablets is not suitable for people with hemochromatosis or renal disorders. This includes patients on dialysis.
- Iron metabolism disorders
- Use in pregnant or breastfeeding women is not recommended.

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).

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

Berocca Mind Tablets use in children under 18 years of age is not recommended.

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.
Thus, patients receiving any other medication or those under medical care should consult a physician or health care professional before taking this medicinal product.

Drug interactions

Active Ingredient	Drug	Description
Vitamin C	Desferrioxamine (medicine used to remove excess iron or aluminium from the body)	Vitamin C may enhance tissue iron toxicity, especially in the heart, causing cardiac decompensation.

Active Ingredient	Drug	Description
	Cyclosporine (immunosuppressive medication)	Antioxidant supplementation including vitamin C may reduce cyclosporine blood level.
	Disulfiram (used to treat chronic alcoholic misuse)	Chronic or high doses of vitamin C may interfere with the effectiveness of the disulfiram.
	Warfarin (blood thinning medicine)	High dose vitamin C may interfere with the effectiveness of warfarin.
Vitamin B_6	Levodopa (prescription medicine used in the treatment of Parkinson's disease)	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 (medicine used to treat rheumatoid arthritis and severe forms of a skin disease called psoriasis)	Folic acid supplementation may reduce the effectiveness of methotrexate in the treatment of acute lymphoblastic leukaemia, and theoretically, the efficacy in the treatment of other cancers.
Magnesium, iron and zinc.	Tetracycline antibiotics	Polyvalent cations, such as magnesium, iron, 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.
	Quinolone antibiotic	
	Penicillamine	
	Biphosphonates	
	Levothyroxine	
	Methyldopa	
	Gastric acid suppressive medications	
	Thiazide diuretics	

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. No studies investigating safety of sage essential oil in fertility and potential of reproductive toxicity have been conducted.

Pregnancy & Breastfeeding

The use of Berocca Mind Tablets is not intended for use during pregnancy and lactation is not recommended.

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

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

Immune system disorders

In isolated cases this product may cause allergic or anaphylactic reaction. Symptoms may include hives, facial swelling, wheezing, skin reddening, rash, blisters, and shock. If an allergic reaction occurs, treatment must be stopped, and a health care professional consulted.

Renal and urinary disorders

Chromaturia (slight yellow discoloration of urine). This effect is harmless and is due to the vitamin B2 contained in the preparation.

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 requested to report any suspected adverse drug reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website. Alternatively, you can report to Bayer SafeTrack site (https://www.safetrack-public.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 Mind 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 of vitamins and minerals are associated with concomitant intake of high dosed single and/or multivitamin preparations.
Uncharacteristic initial symptoms, such as abrupt onset of headache, confusion, and gastrointestinal disturbances such as constipation, diarrhea, nausea, and vomiting might be indicative for an acute overdose.

If such symptoms occur, treatment must be stopped and a health care professional consulted.
Specific clinical manifestations may include the following:

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.

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.

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 B_6
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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.)

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

Salvia Lavandulifolia oil
High doses of Spanish sage may lead to gastrointestinal issues such as nausea, vomiting, or diarrhoea.

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 33.7 (Combination product).
Vitamins and minerals, including trace elements, are essential micronutrients required by every living cells, with key roles in numerous homeostatic processes that enable the body to produce enzymes, hormones and other substances that are essential for energy production, cell maintenance and repair, immune function and recovery from illness, blood formation, and maintenance of vital organs.
Minerals (including trace elements) are inorganic substances and must be taken up through food, whereas vitamins can be synthesized by many species. Humans, however, have lost this ability and cannot synthesize most vitamins in sufficient amounts, and are therefore dependent on a continuous exogenous supply.

Vitamin B1 (thiamine) is active in the form of thiamin pyrophosphate (TPP). As a cofactor, TPP is essential to the activity of cytosolic transketolase and pyruvate dehydrogenase, as well as mitochondrial dehydrogenases, alpha-ketoglutarate dehydrogenase and branched-chain ketoacid dehydrogenase. It is thus essential for converting carbohydrates to energy and needed for normal functioning of muscles, including the heart muscle.

Vitamin B2 (riboflavin) helps in the release of energy from foods. Riboflavin is a precursor to FAD and FMN. As prosthetic groups, they are essential for the activity of flavoenzymes including oxidases, reductases and dehydrogenases.

Vitamin B3 (nicotinamide) promotes release of energy from foods. Niacin is a precursor to reducing groups NAD and nicotinamide adenine dinucleotide phosphate (NADP). These molecules are involved in more than 500 enzymatic reactions, including mitochondrial respiration, glycolysis or even lipid oxidation.

Vitamin B6 (pyridoxine), in the form of pyridoxal phosphate, participates as a coenzyme in numerous enzymes involved in amino acid metabolism (neurotransmitters, niacin, sulfur amino acids), carbohydrate metabolism (glycogen phosphorylase), heme biosynthesis (δ-aminolevulinate), nucleic acid biosynthesis (glycine, one-carbon metabolism), and lipid metabolism (carnitine, phospholipids). During exercise, pyridoxal phosphate is needed for gluconeogenesis and for glycogenolysis in which it serves as a cofactor for glycogen phosphorylase.

Vitamin B12 or cobalamin is the general term for a group of cobalt-containing substances (corrinoids). Vitamin B12 functions as a coenzyme for the methyl transfer reaction that converts homocysteine to methionine, and another reaction that converts L-methyl-malonyl coenzyme A to succinyl coenzyme A. Cobalamin is involved in one-carbon transfer pathways, is part of coenzymes, re-forms folate, and helps to break down some fatty acids and amino acids. It is required for normal erythrocyte production and neurologic function.

Folic acid is a synthetic form of folate from a family of cofactors that carry one-carbon (C1) units required for the synthesis of thymidylate, purines, and methionine, and is required for other methylation reactions. Folate is essential for metabolic pathways involving cell growth, replication and the survival of cells in culture. Thirty to fifty percent of cellular folates are located in the mitochondria. Deficiency symptoms include fatigue and anemia.

Biotin is a prosthetic group for four cellular carboxylases and mostly plays a role in the metabolism of fatty acids and utilization of B-vitamins. An essential role for biotin is also as a keeper of genome expression through biotinylation.

Pantothenic acid is involved in acyl transfer reactions, playing an essential role in energy metabolism. Pantothenic acid is the precursor of CoA, a molecule essential for 4% of all known enzymatic reactions.

Vitamin C is another water-soluble vitamin. It is needed for synthesis of carnitine, which transports long-chain fatty acids into mitochondria, and the catecholamines, epinephrine, and norepinephrine. Ascorbic acid facilitates the transport and uptake of non-heme iron at the mucosa, the reduction of folic acid intermediates, and the synthesis of cortisol. Vitamin C is a potent antioxidant that serves to regenerate vitamin E from its oxidized byproduct. Vitamin C depletion may adversely affect various aspects of physical performance, detrimental effects ranging from nonspecific responses such as fatigue and muscle weakness to anemia. Vitamin C depletion also decreases training because of recurrent injuries to connective tissues and causes decrements in endurance performance as a result of anemia. Historical reports indicate that sailors and soldiers with scurvy (vitamin C deficiency) experienced shortness of breath during physical exertion, and reduced energy and endurance during work.

Magnesium is an intracellular mineral that is essential for the optimal function of a diversity of life-sustaining processes. It serves as a cofactor for more than 300 enzymatic reactions in which food is catabolized and new chemical products are formed; it is required for both aerobic and anaerobic energy production, and for glycolysis as part of the Mg-ATP complex, synthesis of fatty acids and proteins. Magnesium also serves as a regulator of many physiologic functions, including neuromuscular, cardiovascular, immune and hormonal functions, as well as the maintenance of cellular membrane stability.

Iron is a key trace element that is required for the delivery of oxygen to tissues and the use of oxygen at the cellular and subcellular levels. It serves as a functional component of iron-containing proteins including hemoglobin (oxygen transport in the blood), myoglobin (transporting and storing oxygen in the muscle and releasing it when needed during contraction), cytochromes (facilitating transfer of electrons in respiratory chain and is thus importing in ATP synthesis), and specific iron-containing enzymes. Necessary for red blood cell formation and function. Iron deficiency is a problem in females, resulting in reduced physical fitness, weakness, and fatigue. Iron plays a critical role in energy use during work.

Zinc is an important trace element in the body and is involved as a catalyst in more than 200 enzymes. It is a natural constituent of many proteins, hormones, neuropeptides and hormone receptors. Among other reaction, zinc is directly involved in the synthesis of co-enzymes derived from vitamin B6 (pyridoxine). Low zinc status hampers the physiologic functions required for optimal work performance. Low zinc intakes and reduced serum zinc concentrations have been associated with impaired muscle function, including reduced strength and increased propensity to fatigue, and decreased power output during peak work capacity testing. Thus, low zinc status may lead to reduced physical function and performance.

Salvia Lavandulifolia oil. The medicinal use of members of the Salvia genus in terms of their beneficial central nervous system effects, specifically on mood and memory, has developed independently over the millennia. Salvia lavandulaefolia has been used as a traditional herbal remedy in ancient Greek and Roman, Ayurvedic, Native American, and Chinese folk medicines to treat a wide variety of ailments. In Europe their use has been extensively documented since medieval times. Recently, extensive research has been conducted on Salvia plants and the potential benefit that this botanical ingredient may have on cognition.

5.2. Pharmacokinetic properties

Vitamin B_1 (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 B_1 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 B_1 is excreted in the urine. In addition to free vitamin B_1 and a small amount of thiamin diphosphate, thiochrome, and thiamin disulfide, about 20 or more metabolites of vitamin B_1 have been reported in the urine of rats and humans but only six have really been identified. The relative proportion of metabolites to vitamin B_1 excreted increases with decreasing vitamin B_1 intake.

Vitamin B_2 (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 hours in normal adults. In riboflavin deficiency this decreases to 40-70 µg per 24 hours.

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.

Vitamin B3 (Nicotinamide):

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.

Pantothenic acid (Vitamin B_5):
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 acetylcholine; 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.

Vitamin B_6 (Pyridoxine):
Absorption:
Vitamin B_6 is readily absorbed via the gastrointestinal tract after oral doses. Vitamin B_6 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 B_6 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 B_6 is found in phosphorylase, the enzyme that converts glycogen to glucose-1-phosphate. Approximately half the vitamin B_6 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 theerythrocyte 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 B_6 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 B_{12} (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 B_{12} 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.

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 around 1500 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 biotin sulfone. The catabolism of biotin-containing holocarboxylases can lead to biocytin, from which biotin can be liberated by biotinidase, leading to an 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.

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.

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.

***Salvia Lavandulifolia* oil:**
Absorption:
The active compounds in Spanish sage are generally well-absorbed in the gastrointestinal tract after ingestion.
Distribution:
Once absorbed, these compounds are distributed throughout the body, including the brain, where they can exert their effects on cognition.
Metabolism:
The metabolism of Spanish sage involves hepatic enzymes, and the specific pathways can vary based on the individual's metabolic rate and the form of the herb consumed.
Excretion:
The metabolites of Spanish sage are typically excreted through urine. The half-life of the active components can vary, influencing how long the effects last.

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

Cellulose microcrystalline
Partially pregelatinized starch
Magnesium stearate
Calcium carbonate
Isomalt
Hydroxypropylmethylcellulose
Medium chain triglycerides
Copper chlorophyllin

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

24 months

6.4. Special precautions for storage

Store at or below 25°C.
Keep in the original package.

6.5. Nature and contents of container

Berocca Mind Tablets is presented as film coated tablets packaged in blisters made from a three-layer thermoforming foil, consisting of rigid polyvinylchloride (PVC) laminated with ThermoElast (TE) and coated with polyvinylidene chloride (PVDC), providing high water vapor barrier properties. The blister is sealed with a hard tempered aluminium lid foil, coated with a heat-sealing layer compatible with PVC and PVDC. The immediate container is designed to ensure product integrity and is available in packs of 30's, 60's, and 90's. Additionally, the blister packs are placed in a non-functional secondary packaging, such as a folding carton, which may include a leaflet.
Not all pack sizes may be available.

6.6. Special precautions for disposal

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Bayer (Pty) Ltd
Collaboration Hub
1st Floor, Waterfall Circle
9 Country Estate Drive
Waterfall City
Midrand, 2090
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

TBC

11. DATE OF FIRST AUTHORISATION/ RENEWAL OF THE AUTHORISATION

To be confirmed upon registration.

Manufacturer:
Bayer Indonesia Cimanggis, Jl. Raya Bogor No.32, Cisalak, Kec. Sukmajaya, Kota Depok, Jawa Barat 16416, Indonesia.