SmPC (Summary of Product Characteristics)

1. Name of the medicinal Product

Krishat Multivitamins & Minerals with Ginseng soft gelatin Capsules

2. Qualitative and Quantitative Composition

Each hard gelatin capsules contains:

Vitamin A (As Palmitate)	BP	2500	IU
Vitamin B1 (Thiamine Monohydrate)	BP	1	mg
Vitamin B2 (Riboflavin)	BP	1	mg
Vitamin B6	BP	0.5	mg
Vitamin B3 (Nicotinamide)	BP	15	mg
Vitamin E	BP	5	mg
Folic Acid	BP	50	mcg
Calcium (From Di-basic Calcium Phosphate)	BP	75	mg
Phosphorous (From Di-basic Calcium Phosphate)	BP	58	mg
Iron (From Ferrous Sulphate)	BP	5	mg
Copper (From Copper Sulphate Anhydrous)	BP	0.45	mg
Magnesium (From Magnesium Sulphate)	BP	3	mg
Manganese (From Magnesium Sulphate)	BP	0.05	mg
Zinc (As Zinc Sulphate)	BP	0.15	mg
Potassium (From Potassium Sulphate)	BP	2	mg
Iodine (From Potassium Iodide)	BP	0.075	mg
Ginseng Extract Powder JP	BP	990	mcg
Vitamin B12	BP	1	mcg
Vitamin D3	BP	200	IU
Excipients			q.s.
Approved colours used in capsule shell			

Quantitative declaration

Excipients with known effect:
Butylated Hydroxy Anisole, Butylated Hydroxy Toluene, Beeswax, Hydrogenated Vegetable Oil, Soya lecithin, Refined Soybean oil, Gelatin, Glycerin, Sorbitol 70%, Methyl Paraben, Propyl Paraben, colour: Titanium Dioxide, colour: Ponceau 4R Supra, colour: Black Iron Oxide, Liquid paraffin, Dibasic Calcium Phosphate & Colloidal anhydrous silica (Aerosil).
For a full list of excipients, see section 6.1

3. Pharmaceutical Form

Oral Capsules

A red and Black coloured, oblong shaped soft gelatin capsule filled with light brown coloured medicament.

4. Clinical Particulars

4.1 Therapeutic Indications

As a therapeutic nutritional adjunct where the intake of vitamins and minerals is suboptimal, e.g. in the presence of organic disease such as malignancy and immune deficiency syndromes, such as AIDS.

As a therapeutic nutritional adjunct in conditions where the absorption of vitamins and minerals is suboptimal, e.g. malabsorption, inflammatory bowel disease and fistulae, short bowel syndrome and Crohn's disease, and where concurrent medication decreases vitamin and mineral absorption.

As a therapeutic nutritional adjunct in convalescence from illness, e.g. where anorexia or cachexia exists and following chemo- or radio-therapy.

As a therapeutic nutritional adjunct in convalescence from surgery, e.g. where nutritional intake continues to be inadequate.

As a therapeutic nutritional adjunct for patients on special or restricted diets, e.g. in renal diets and where several food groups are restricted in therapeutic weight reducing diets.

As a therapeutic nutritional adjunct where food intolerance exists, e.g. exclusion diets.

As an adjunct in synthetic diets, e.g. in phenylketonuria, galactosaemia and ketogenic diets.

4.2 Posology and Method of Administration

Posology

Adults and the Elderly

One capsule daily, preferably taken one hour after meals. Do not exceed the stated dose. The capsule should be swallowed whole with water.

Children under 12 years of age

Krishat Multivitamins & Minerals with Ginseng soft gelatin Capsules are not recommended for this age group.

4.3 Contraindications

Hypercalcaemia, haemochromatosis and other iron storage disorders.

Hypersensitivity to the active substance(s) or to any of the excipients.

Krishat Multivitamins & Minerals with Ginseng soft gelatin Capsules contain soya bean oil. Patients allergic to peanut or soya should not take this medicine.

4.4 Special Warnings and Special Precautions for Use

Whilst taking Krishat Multivitamins & Minerals with Ginseng soft gelatin Capsules both protein and energy are also required to provide complete nutrition in the daily diet. No other vitamins, minerals or supplements with or without vitamin A should be taken with this preparation except under medical supervision.

Do not take Krishat Multivitamins & Minerals with Ginseng soft gelatin Capsules on an empty stomach. Do not exceed the stated dose. Keep out of the reach of children. If symptoms persist, consult your doctor.

Important warning: Contains iron. Keep out of the reach and sight of children, as overdose may be fatal.

This medicine contains black oxide of iron and E124 (ponceau 4R red) which may cause allergic reactions.

Evidence from Randomised Control Trials suggests that high doses (20-30 mg/day) b-carotene intake may increase the risk of lung cancer in current smokers and those previously exposed to asbestos. This high-risk population should consider the potential risks and benefits of Krishat Multivitamins & Minerals with Ginseng soft gelatin Capsules, which contain 4.5mg per recommended daily dose, before use.

Patients with thyroid disorders should seek medical advice before taking Krishat Multivitamins & Minerals with Ginseng soft gelatin Capsules. An allowance should be made for vitamins or minerals obtained from other sources.

4.5 Interaction with other medicinal products and other forms of interaction

Folic acid can reduce the plasma concentration of phenytoin. Oral iron and zinc sulfate reduce the absorption of tetracyclines.

4.6 Fertility, Pregnancy and Lactation

Krishat Multivitamins & Minerals with Ginseng soft gelatin Capsules may be administered during pregnancy and lactation at the recommendation of the physician.

4.7 Effects on ability To Drive and use Machines

None anticipated

4.8 Undesirable Effects

Assessment of undesirable effects is based on the following frequency groupings:

Very common: ≥ 1/10

Common: ≥ 1/100 to <1/10

Uncommon: ≥ 1/1,000 to <1/100

Rare: ≥ 1/10,000 to <1/1,000

Very rare: <1/10,000

Not known: cannot be estimated from the available data

Immune system disorders	*Not known:* Hypersensitivity reaction (such as rash)
Gastrointestinal disorders	*Not known:* Gastrointestinal disturbances (such as nausea, vomiting and abdominal pain)

4.9 Overdose

No cases of overdosage due to Krishat Multivitamins & Minerals with Ginseng soft gelatin Capsules therapy have been reported. Any symptoms which may be observed due to the ingestion of large quantities of Krishat Multivitamins & Minerals with Ginseng soft gelatin Capsules will be due to the fat soluble vitamin content. If iron overdosage is suspected, symptoms may include nausea, vomiting, diarrhoea, abdominal pain, haematemesis, rectal bleeding, lethargy and circulatory collapse. Hyperglycaemia and metabolic acidosis may also occur. Treatment should be implemented immediately. In severe cases, after a latent phase,

relapse may occur after 24 - 48 hours, manifest by hypotension coma and hepatocellular necrosis and renal failure.

Treatment

The following steps are recommended to minimise or prevent further absorption of the medication:

1. Administer an emetic.

2. Gastric lavage may be necessary to remove drug already released into the stomach. This should be undertaken using desferrioxamine solution (2 g/l). Desferrioxamine 5 g in 50 - 100 ml water should be introduced into the stomach following gastric emptying. Keep the patient under constant surveillance to detect possible aspiration of vomitus; maintain suction apparatus and standby emergency oxygen in case of need.

3. A drink of mannitol or sorbitol should be given to induce small bowel emptying.

4. Severe poisoning: in the presence of shock and/or coma with high serum iron levels (>142 µ mol/l) immediate supportive measures plus i.v. infusion of desferrioxamine should be instituted. The recommended dose of desferrioxamine is 5 mg/kg/h by slow i.v. infusion up to a maximum of 80 mg/kg/24 hours. Warning: hypotension may occur if the infusion rate is too rapid.

5. Less severe poisoning: i.m. desferrioxamine 50 mg/kg up to a maximum dose of 4 g should be given.

6. Serum iron levels should be monitored throughout.

5. Pharmacological Properties

5.1 Pharmacodynamics Properties

The following account summarises the pharmacological effects of the vitamins and minerals in Krishat Multivitamins & Minerals with Ginseng soft gelatin Capsules and describes the conditions caused by deficiency of these.

Vitamin A

Vitamin A plays an important role in the visual process. It is isomerised to the 11-cis isomer and subsequently bound to the opsin to form the photoreceptor for vision under subdued light. One of the earliest symptoms of deficiency is night blindness which may develop into the more serious condition xerophthalmia. Vitamin A also participates in the formation and maintenance of the integrity of epithelial tissues and mucous membranes. Deficiency may cause skin changes resulting in a dry rough skin with lowered resistance to minor skin infections. Deficiency of Vitamin A, usually accompanied by protein-energy malnutrition, is linked with a frequency of infection and with defective immunological defence mechanisms.

Vitamin D

Vitamin D is required for the absorption of calcium and phosphate from the gastro-intestinal tract and for their transport. Its involvement in the control of calcium metabolism and hence the normal calcification of bones is well documented. Deficiency of Vitamin D in children may result in the development of rickets.

Vitamin B_1 (Thiamine)

Thiamine (as the coenzyme, thiamine pyrophosphate) is associated with carbohydrate metabolism. Thiamine pyrophosphate also acts as a co-enzyme in the direct oxidative pathway

of glucose metabolism. In thiamine deficiency, pyruvic and lactic acids accumulate in the tissues. The pyruvate ion is involved in the biosynthesis of acetylcholine via its conversion to acetyl co-enzyme A through a thiamine-dependent process. In thiamine deficiency, therefore, there are effects on the central nervous system due either to the effect on acetylcholine synthesis or to the lactate and pyruvate accumulation. Deficiency of thiamine results in fatigue, anorexia, gastro-intestinal disturbances, tachycardia, irritability and neurological symptoms. Gross deficiency of thiamine (and other Vitamin B group factors) leads to the condition beri-beri.

Vitamin B_2 (Riboflavine)

Riboflavine is phosphorylated to flavine mononucleotide and flavine adenine dinucleotide which act as co-enzymes in the respiratory chain and in oxidative phosphorylation. Riboflavine deficiency presents with ocular symptoms, as well as lesions on the lips and at angles of the mouth.

Vitamin B_6 (Pyridoxine)

Pyridoxine, once absorbed, is rapidly converted to the co-enzymes pyridoxal phosphate and pyridoxamine phosphate which play an essential role in protein metabolism. Convulsions and hypochromic anaemia have occurred in infants deficient in pyridoxine.

Vitamin B_{12} (Cyanocobalamin)

Vitamin B_{12} is present in the body mainly as methylcobalamin and as adenosylcobalamin and hydroxocobalamin. These act as co-enzymes in the trans methylation of homocysteine to methionine; in the isomerisation of methylmalonyl co-enzyme to succinyl co-enzyme and with folate in several metabolic pathways respectively. Deficiency of Vitamin B_{12} interferes with haemopoiesis and produces megaloblastic anaemia.

Vitamin E

Vitamin E deficiency has been linked to disorders such as cystic fibrosis where fat absorption is impaired. It is essential for the normal function of the muscular system and the blood.

Nicotinamide

The biochemical functions of nicotinamide as NAD and NADP (nicotinamide adenine dinucleotide phosphate) include the degradation and synthesis of fatty acids, carbohydrates and amino acids as well as hydrogen transfer. Deficiency produces pellagra and mental neurological changes.

Calcium (Calcium Hydrogen Phosphate)

Calcium is an essential body electrolyte. It is involved in the maintenance of normal muscle and nerve function and essential for normal cardiac function and the clotting of blood. Calcium is mainly found in the bones and teeth. Deficiency of calcium leads to rickets, osteomalacia in children and osteoporosis in the elderly.

Phosphorus (Calcium Hydrogen Phosphate)

Phosphate plays important roles in the osteoblastic and osteoclastic reactions. It interacts with calcium to modify the balance between these two processes. Organic phosphate esters play a key role in the metabolism of carbohydrates, fats and proteins and in the formation of 'high energy phosphate' compounds. Phosphate also acts as a buffer and plays a role in the renal excretion of sodium and hydrogen ions.

Folic Acid

Folic acid is reduced in the body to tetrahydrofolate which is a co-enzyme for various metabolic processes, including the synthesis of purine and pyrimidine nucleotides and hence in

the synthesis of DNA. It is also involved in some amino acid conversion and in the formation and utilisation of formate. Deficiency of folic acid leads to megaloblastic anaemia.

Iron

Iron, as a constituent of haemoglobin, plays an essential role in oxygen transport. It is also present in the muscle protein myoglobin and in the liver. Deficiency of iron leads to anaemia.

Copper (Copper Sulfate)

Traces of copper are essential to the body as constituents of enzyme systems involved in oxidation reactions.

Magnesium (Magnesium Oxide)

Magnesium is essential to the body as a constituent of skeletal structures and in maintaining cell integrity and fluid balance. It is utilised in many of the functions in which calcium is concerned but often exerts the opposite effect. Some enzymes require the magnesium ion as a co-factor.

Potassium (Potassium Sulfate)

Potassium is the principle cation of intracellular fluid and is intimately involved in the cell function and metabolism. It is essential for carbohydrate metabolism and glycogen storage and protein synthesis and is involved in transmembrane potential where it is necessary to maintain the resting potential in excitable cells. Potassium ions maintain intracellular pH and osmotic pressure. Prolonged or severe diarrhoea may lead to potassium deficiency.

Zinc (Zinc Sulfate)

Zinc is a constituent of many enzymes and is, therefore, essential to the body. It is present with insulin in the pancreas. It plays a role in DNA synthesis and cell division. Reported effects of deficiency include delayed puberty and hypogonadal dwarfism.

Manganese (Manganese Sulfate)

Manganese is a constituent of enzyme systems including those involved in lipid synthesis, the tricarboxylic acid cycle and purine and pyrimidine metabolism. It is bound to arginase of the liver and activates many enzymes.

Iodine (Potassium Iodide)

Iodine is an essential constituent of the thyroid hormones.

Ginseg

Many reports have indicated that they have used herbal medicines, and ginseng is one of the most popular herbs. Several recent reports have indicated that the antioxidant/antioxidative stress activities of ginseng play a role in the benefits of ginseng; however, the precise mechanism is lacking. The antioxidant response element (ARE) is a critical regulatory element for the expression of many antioxidant enzymes and phase II/III drug metabolizing/transporter genes, mediated by the transcription factor nuclear factor (erythroid-derived 2)-like 2 (Nrf2). The aim of this study was to examine the potential activation and synergism of Nrf2-ARE-mediated transcriptional activity between three common ginsenosides present in ginseng, ginsenoside Rb1 (Rb1), ginsenoside Rg1 (Rg1), and ginsenoside 20(S)-protopanaxatriol (20S). We tested whether these ginsenosides and their combinations could induce Nrf2-ARE activities in HepG2-C8 cells with stably transfected ARE luciferase reporter gene. Cell proliferation, antioxidant and ARE activities, Western blotting of Nrf2 protein, and qPCR of mRNA of Nrf2 were conducted for Rb1, Rg1, and 20S as well as the combinations of 20S with Rb1 or Rg1. To determine the combination effects, the combination index (CI) was calculated. Rb1 and Rg1 are relatively nontoxic to the cells, while 20S at 50 μM or above significantly inhibited the cell

proliferation. Rb1, Rg1, or 20S induced total antioxidant activity and ARE activity in a concentration-dependent manner. Furthermore, combinations of 20S with either Rb1 or Rg1 induced total antioxidant and ARE activity synergistically. The induction of Nrf2 protein and mRNA was also found to be synergistic with the combination treatments. In summary, in this study, we show that ginsenosides Rb1, Rg1, and 20S possess antioxidant activity, transcriptionally activating ARE as well as the potential of synergistic activities. The Nrf2-ARE-mediated antioxidant pathway could play a role for the overall antioxidative stress activities, which could be important for ginseng's health beneficial effects such as cancer chemopreventive activities.

5.2 Pharmacokinetic Properties

The following account describes the absorption and fate of each of the active constituents of Krishat Multivitamins & Minerals with Ginseng soft gelatin Capsules.

Vitamin A

Except when liver function is impaired, Vitamin A is readily absorbed. β -carotene (as in Krishat Multivitamins & Minerals with Ginseng soft gelatin Capsules) is Provitamin A and is the biological precursor to Vitamin A. It is converted to Vitamin A (Retinol) in the liver; retinol is emulsified by bile salts and phospholipids and absorbed in a micellar form. Part is conjugated with glucuronic acid in the kidney and part is metabolised in the liver and kidney, leaving 30 to 50% of the dose for storage in the liver. It is bound to a globulin in the blood. Metabolites of Vitamin A are excreted in the faeces and the urine.

Vitamin D

The metabolism of ergocalciferol is similar to that of cholecalciferol. Cholecalciferol is absorbed from the gastro-intestinal tract into the circulation. In the liver, it is hydroxylated to 25-hydroxycholecalciferol, is subject to entero-hepatic circulation and is further hydroxylated to 1,25-dihydroxycholecalciferol in the renal tubule cells. Vitamin D metabolites are bound to specific plasma proteins.

Vitamin B_1 (Thiamine)

Thiamine is absorbed from the gastro-intestinal tract and is widely distributed to most body tissues. Amounts in excess of the body's requirements are not stored but excreted in the urine as unchanged thiamine or its metabolites.

Vitamin B_2 (Riboflavine)

Riboflavine is absorbed from the gastro-intestinal tract and in the circulation is bound to plasma proteins. It is widely distributed. Little is stored and excess amounts are excreted in the urine. In the body riboflavine is converted to flavine mononucleotide (FMN) and then to flavine adenine dinucleotide (FAD).

Vitamin B_6 (Pyridoxine)

Pyridoxine is absorbed from the gastro-intestinal tract and converted to the active pyridoxal phosphate which is bound to plasma proteins. It is excreted in the urine as 4-pyridoxic acid.

Vitamin B_{12} (Cyanocobalamin)

Cyanocobalamin is absorbed from the gastro-intestinal tract and is extensively bound to specific plasma proteins. A study with labelled Vitamin B_{12} showed it was quickly taken up by the intestinal mucosa and held there for 2 - 3 hours. Peak concentrations in the blood and tissues did not occur until 8 - 12 hours after dosage with maximum concentrations in the liver within 24 hours. Cobalamins are stored in the liver, excreted in the bile and undergo enterohepatic recycling. Part of a dose is excreted in the urine, most of it in the first eight hours.

Vitamin E

Vitamin E is absorbed from the gastro-intestinal tract. Most appears in the lymph and is then widely distributed to all tissues. Most of a dose is slowly excreted in the bile and the remainder is eliminated in the urine as glucuronides of tocopheronic acid or other metabolites.

Nicotinamide (Nicotinic Acid Amide)

Nicotinic acid is absorbed from the gastro-intestinal tract, is widely distributed in the body tissues and has a short half-life.

Calcium (Calcium Hydrogen Phosphate)

A third of ingested calcium is absorbed from the small intestine. Absorption of calcium decreases with age.

Phosphorus (Calcium Hydrogen Phosphate)

The body contains from 600 - 800 g of phosphorus, over 80% of which is present in the bone as phosphate salts, mainly hydroxyapatite crystals. The phosphate in these crystals is available for exchange with phosphate ions in the extra-cellular fluids.

Folic Acid

Folic acid is absorbed mainly from the proximal part of the small intestine. Folate polyglutamates are considered to be deconjugated to monoglutamates during absorption. Folic acid rapidly appears in the blood where it is extensively bound to plasma proteins. Some folic acid is distributed in body tissues, some is excreted as folate in the urine and some is stored in the liver as folate.

Selenium

Although it has been established that selenium is essential to human life, very little information is available on its function and metabolism.

Ferrous Sulphate (Iron)

Iron is absorbed chiefly in the duodenum and jejunum. Absorption is aided by the acid secretion of the stomach and if the iron is in the ferrous state as in ferrous Sulfate. In conditions of iron deficiency, absorption is increased and, conversely, it is decreased in iron overload. Iron is stored as ferritin.

Copper Sulfate (Copper)

Copper is absorbed from the gastro-intestinal tract and its major route of excretion is in the bile.

Magnesium Sulphate (Magnesium)

Magnesium salts are poorly absorbed from the gastro-intestinal tract; however, sufficient magnesium will normally be absorbed to replace deficiency states. Magnesium is excreted in both the urine and the faeces but excretion is reduced in deficiency states.

Potassium Sulfate (Potassium)

Potassium salts are absorbed from the gastro-intestinal tract. Potassium is excreted in the urine, the faeces and in perspiration. Urinary excretion of potassium continues even when intake is low.

Zinc Sulfate (Zinc)

Zinc is poorly absorbed from the gastro-intestinal tract. It is widely distributed throughout the body. It is excreted in the faeces with traces appearing in the urine.

Manganese Sulfate (Manganese)

Manganese salts are poorly absorbed.

Potassium Iodide (Iodine)

Iodides are absorbed and stored in the thyroid gland as thyroglobulin. Iodides are excreted in the urine with smaller amounts appearing in the faeces, saliva and sweat.

Ginseng

Various in vivo and clinical studies have identified the pharmacokinetics of various ginseng saponin compounds. However, the pharmacokinetic activities of ginseng and ginsenosides are still not clearly understood because of their heterogeneous and diversified chemical structures. Studies have revealed that absorption of ginseng saponins is low when they are administered orally; they have low membrane permeability and are extensively metabolized in the gastrointestinal tract. Ginsenosides Rg1, Re, and Rh1 and R1 saponins show better bioavailability than ginsenosides Ra3, Rb1, Rd, Rg3, and Rh2 saponins. In humans, the half-lives (T1/2) of saponins are usually less than 24 hours. Possible drug interactions have been reported between *P. ginseng* and warfarin, phenelzine, and alcohol.

5.3 Preclinical Safety Data

No other relevant preclinical data is available.

6. Pharmaceutical Particulars

6.1 List of Excipients

Butylated Hydroxy Anisole, Butylated Hydroxy Toluene, Beeswax, Hydrogenated Vegetable Oil, Soya lecithin, Refined Soybean oil, Gelatin, Glycerin, Sorbitol 70%, Methyl Paraben, Propyl Paraben, colour: Titanium Dioxide, colour: Ponceau 4R Supra, colour: Black Iron Oxide, Liquid paraffin, Dibasic Calcium Phosphate & Colloidal anhydrous silica (Aerosil).

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

36 months

6.4 Special Precautions for Storage

Store below 30°C. Protect from light & moisture.

6.5 Nature and Contents of Container

The 15 soft gelatin capsules are packed in Alu/PVC blister and inserted in a carton. Pack sizes: 2x15 capsules.

6.6 Special precaution for disposal and other handling

Any unused product or waste material should be disposed of in accordance with local requirements.

Keep the medicine out of reach of children

7. Manufacturing By

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