COGNIMOM®

SUBMITTED BY: NUTRI-LAB NIGERIA LTD.

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SUMMARY OF PRODUCT CHARACTERISTICS

(SmPC) .

1. NAME OF THE DRUG PRODUCT

Cognimom®

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Pink, round-shaped, biconvex film-coated tablets.

Each tablet contains:

Dry Vitamin A (as Retinyl Acetate) B.P.……800 mcg

Vitamin D (as Cholecalciferol) B.P.……5 mcg

Vitamin E (as D-alpha Tocopheryl Succinate)……10 mg

Vitamin C (as Ascorbic Acid)……70 mg

Vitamin B_1 (Thiamine Mononitrate) B.P.……1.4 mg

Vitamin B_2 (Riboflavin) B.P……1.4 mg

Niacin (as Niacinamide) BP ……18 mg

Vitamin B_6 (as Pyridoxine HCl) B.P……1.9 mg

Vitamin B_{12} (as Cyanocobalamin) B.P……2.6 mcg

Folate (as Folic Acid) B.P……400 mcg

Iron (Ferrous Fumarate) B.P……30 mg

Zinc (Zinc Oxide) B.P……15 mg

Copper (Copper Oxide) B.P……2 mg

Selenium (Sodium Selenite) B.P……65 mcg

Iodine (Potassium Iodide) B.P……150 mcg

Excipients……q.s

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Oral prophylactic and therapeutic treatment of vitamins and minerals deficiencies. Cognimom® is also indicated for healthy body, growth, good appetite, convalescence, and all conditions where there is need to withstand stress and increased demands.

4.2 Posology and method of administration

Prophylactic

Adults and children over 12 years

One tablet daily

Or as prescribed by a physician

4.3 Contradindications

Known sensitivity to any of the ingredients.

4.4 Special warnings and precautions for use

No special warnings.

4.5 Interaction with other drug products and other forms of interaction

Effect of other medicinal products on cholecalciferol:

Inducers of CYP450 metabolic enzymes such as rifampicin, carbamazepine, phenytoin, barbiturates (e.g. phenobarbital, primidone) and glucocorticoids may reduce the efficacy of vitamin D due to increased inactivation. Concomitant use of these medicinal products can increase the vitamin D requirement.

Isoniazid may reduce the effectiveness of vitamin D3 due to inhibition of the metabolic activation of vitamin D. Medicinal products leading to fat malabsorption, e.g. orlistat and cholestyramine, may impair the absorption of vitamin D. Increased parathyroid hormone levels can increase the vitamin D metabolism and thus increase the vitamin D requirement.

Concomitant treatment with cardiac glycosides can increase their toxicity due to hypercalcaemia (risk of arrhythmias). Strict medical supervision is needed and, if necessary monitoring of ECG and serum calcium levels.

Concomitant use of thiazide-type diuretics increases the risk of hypercalcaemia as they reduce the urinary elimination of calcium. In this case, serum calcium levels should be regularly monitored.

Magnesium-containing medicines (e.g. antacids) should not be used during therapy as this may lead to hypermagnesaemia.

Vitamin D3 might increase the intestinal absorption of aluminium.

The pyridoxine hydrochloride may reduce the effectiveness of levodopa.

The following interactions are known for potassium iodide:

Potassium-sparing diuretics: Concomitant use of potassium iodide and potassium-sparing diuretics produces a reduction in renal excretion of potassium that can lead to serious hyperkalemia (arrhythmias) or even fatal (heart attack), being the existence of reduced kidney function a predisposing factor for the occurrence of this complication. If you have to administer both drugs at the same time, it is necessary to monitor potassium levels and adjust dose accordingly. In any case, should be avoided this type of combination.

Lithium salts: Concomitant use of lithium salts with potassium salts may result in hypothyroidism. Therefore, this combination should be avoided whenever possible. However, in case it is necessary to administer both drugs and develop hypothyroidism, thyroid hormone can be used to treat symptoms.

Antithyroidal drugs: Concomitant use of antithyroidal agents and potassium iodide can produce additive hypothyroid effects.

Iron reduces the absorption of penicillamine, bisphosphonates, ciprofloxacin, entacapone, levodopa, levofloxacin, levothyroxine (thyroxine) (give at least 2 hours apart), moxifloxacin, mycophenolate, norfloxacin, ofloxacin, zinc. Absorption of both iron and antibiotic may be reduced if Fersamal is given with tetracycline.

Absorption of oral iron is reduced by calcium salts, Magnesium salts (as magnesium trisilicate), Trientine.

Chloramphenicol delays plasma iron clearance, incorporation of iron into red blood cells and interferes with erythropoiesis. Some inhibition of iron absorption may occur if it is taken with cholestyramine, tea, eggs or milk.

Avoid concomitant use of iron with dimercaprol.

Oral iron antagonises hypotensive effect of methyldopa.

4.6 Fertility, pregnancy and lactation

Considered safe in the recommended dose.

4.7 Effects on ability to drive and use machines

None stated

4.8 Undesirable effects

None known

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions to the regulatory bodies such as NAFDAC.

4.9 Overdose

Not applicable

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Vitamin A (as Retinyl Acetate)
Vitamin A is required for growth and bone development, vision, reproduction and the integrity of mucosal and epithelial surfaces. In the retina, retinol is converted to the aldehyde, cis-retinal, which combines with opsin to form rhodopsin, the visual pigment.

Vitamin D (as Cholecalciferol)
Cholecalciferol is produced within the skin under the influence of UV radiation including sunlight. In its biologically active form, Cholecalciferol stimulates intestinal calcium absorption, incorporation of calcium into the osteoid, and release of calcium from bone tissue. In the small intestine it promotes rapid and delayed calcium uptake. The passive and active transport of phosphate is also stimulated. In the kidney, it inhibits the excretion of calcium and phosphate by promoting tubular resorption. The production of parathyroid hormone (PTH) in the parathyroids is inhibited directly by the biologically active form of Cholecalciferol. PTH secretion is inhibited additionally by the increased calcium uptake in the small intestine under the influence of biologically active Cholecalciferol.

Vitamin E (as D-alpha Tocopheryl Succinate)

Alpha-tocopherol is the predominant form of vitamin in human and animal tissues, and it has the highest bioavailability. This is because the liver preferentially resecretes only alpha-tocopherol by way of the hepatic alpha-tocopherol transfer protein (alpha-TTP); the liver metabolizes and excretes all the other vitamin E variants, which is why blood and cellular concentrations of other forms of vitamin E other than alpha-tocopherol are ultimately lower.

Furthermore, the term alpha-tocopherol generally refers to a group of eight possible stereoisomers which is often called all-rac-tocopherol for being a racemic mixture of all eight stereoisomers. Of the eight stereoisomers, the RRR-alpha-tocopherol - or sometimes referred to as the d-alpha-tocopherol - stereoisomer is the naturally occurring form of alpha-tocopherol that is perhaps best recognized by the alpha-TTP and has been reported to demonstrate approximately twice the systemic availability of all-rac-tocopherol.

As a result, often times (but certainly not always) the discussion of vitamin E - at least within the context of using the vitamin for health-related indications - is generally in reference to the use of RRR- or d-alpha-tocopherol.

Subsequently, without further evidence to suggest otherwise, alpha-tocpherol succinate is generally believed to undergo a logical de-esterification in the gastrointestinal tract before being subsequently absorbed as free tocopherol.

Vitamin C

Vitamin C is essential to humans. Its components, ascorbic acid and dehydroascorbic acid, form an important redox system.
Ascorbic acid has special functions in this redox interrelationship, as an antioxidant and enzyme cofactor, which plays a crucial role in various hydroxylation reactions. There are several ascorbate- dependent mono- and dioxygenations in various neurotransmitter and hormone formation processes, and ascorbate is also required for the hydroxylation of carnitine. It has been suggested that carnitine deficiency is responsible for the early symptoms of scurvy. Vitamin C has certain biological functions that can influence energy production and thus physical performance. In addition to its role for synthesis of collagen and carnitine, which transports long-chain fatty acids into mitochondria, vitamin C is also needed for synthesis of 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 product.

Vitamin B Complex.

Vitamin B_1 is essential for proper carbohydrate metabolism and plays an essential role in the decarboxylation of alpha keto acid.
Riboflavin is essential for the utilisation of energy from food. It is a component of co-enzymes which play an essential role in oxidative/ reductive metabolic reactions. Riboflavin is also necessary for the functioning of pyridoxine and nicotinic acid.
Niacin (as Niacinamide): Niacin can decrease lipids and apolipoprotein B (apo B)-containing lipoproteins by modulating triglyceride synthesis in the liver, which degrades apo B, or by modulating lipolysis in adipose tissue. Niacin inhibits hepatocyte diacylglycerol acyltransferase-2. Converted to Nicotinamide Adenine Dinucleotide and Nicotinamide Adenine Dinucleotide Phosphate in the body, both of which are co-enzymes important in electron transfer in respiratory reactions.

Vitamin B_{12} is a coenzyme involved in the metabolism of every cell of the human body, especially affecting DNA synthesis and regulation, but also fatty acid metabolism and amino acid metabolism.

Folic acid is an essential cofactor for enzymes involved in DNA and RNA synthesis. More specifically, folic acid is required by the body for the synthesis of purines, pyrimidines, and methionine before incorporation into DNA or protein. Folic acid is the precursor of tetrahydrofolic acid, which is involved as a cofactor for transformylation reactions in the biosynthesis of purines and thymidylates of nucleic acids. Impairment of thymidylate

synthesis in patients with folic acid deficiency is thought to account for the defective deoxyribonucleic acid (DNA) synthesis that leads to megaloblast formation and megaloblastic and macrocytic anemias. Folic acid is particularly important during phases of rapid cell division, such as infancy, pregnancy, and erythropoiesis, and plays a protective factor in the development of cancer. As humans are unable to synthesize folic acid endogenously, diet and supplementation is necessary to prevent deficiencies. In order to function properly within the body, folic acid must first be reduced by the enzyme dihydrofolate reductase (DHFR) into the cofactors dihydrofolate (DHF) and tetrahydrofolate (THF). This important pathway, which is required for de novo synthesis of nucleic acids and amino acids, is disrupted by anti-metabolite therapies such as Methotrexate as they function as DHFR inhibitors to prevent DNA synthesis in rapidly dividing cells, and therefore prevent the formation of DHF and THF.

Iron is an essential constituent of the body, and is necessary for haemoglobin formation and for the oxidative processes of living tissues. Iron and iron salts should be given for the treatment or prophylaxis of iron deficiency anaemias. Preparations of iron are administered by mouth, by intramuscular or intravenous injection.

Soluble ferrous salts are most effective by mouth. Ferrous fumarate is an easily absorbed source of iron for replacement therapy. It is a salt of ferrous iron with an organic acid and is less irritant to the gastro-intestinal tract than salts with inorganic acids.

Zinc is component of many metalloenzymes.example: red blood cell carbonic anhydrase, alkaline phosphatase ,alcohol dehydrogenase, carboxy-peptidase, SOD (cytosol), and many enzymes involved in RNA and DNA synthesis, such as DNA and RNA polymerases.
Copper is absorbed from the gut via high affinity copper uptake protein and likely through low affinity copper uptake protein and natural resistance-associated macrophage protein-2 [4]. It is believed that copper is reduced to the Cu1+ form prior to transport. Once inside the enterocyte, it is bound to copper transport protein ATOX1 which shuttles the ion to copper transporting ATPase-1 on the golgi membrane which take up copper into the golgi apparatus. Once copper has been secreted by enterocytes into the systemic circulation it remain largely bound by ceruloplasmin (65-90%), albumin (18%), and alpha 2-macroglobulin (12%).

Selenium is an essential trace element. In human, selenium compounds are glutathione peroxidase and a selenium protein P found in the plasma. In both these proteins, selenium is protein-bound and is present in the form of the amino acid selenocysteine. Other selenium-dependent enzymes are the thioredoxine-reductase and the 5'-deiodinase that catalyses the conversion from tetraiodothyronine (T4) to the active thyroid hormone triiodothyronine (T3).

The selenium-containing glutathionperoxidase is a part of the anti-oxidative protection system of the mammal cell. In case of sufficient quantities of reduced glutathione, the glutathionperoxidase converts a variety of hydroperoxides into relevant alcohols.

The patho-physiological relevance of selenium-dependent reactions has been demonstrated by observations in selenium deficiency. The selenium-containing glutathionperoxidase affects the leucotriene, thromboxane and prostacyclin metabolism. Selenium deficiency inhibits reactions of the immune system, especially the non-specific, cell-bound and humoral reactions. Selenium deficiency affects the activity of a few liver enzymes. Selenium deficiency potentiates oxidatively or chemically induced liver damage and toxicity of heavy metals such as quicksilver and cadmium.

Deficiency of selenium has been associated with an endemic form of cardiomyopathy, Keshan disease. It has also been associated with Kaschin-Beck disease, an endemic osteoarthropathy which causes a severe deformity of the joints.

Clinically manifested selenium deficiency has also been seen to be a result of long-term parenteral nutrition and unbalanced diets. Cardiomyopathies and myopathies are observed most frequently.

The iodine content of the thyroid gland is related generally to the intake of iodine. In those situations where iodine supplements have been abundant, the thyroid may contain 10-20 mg, but in situations of chronic iodine deficiency the thyroid may contain only quantities of 200 micrograms. Therefore, a sufficiently severe iodine deficiency can affect thyroid hormone synthesis during this critical period and cause hypothyroidism and brain damage. The clinic consequence will be a mental retardation.

The anti-goitrogenic effect of potassium iodide is due to inhibition of thyroid protein biosynthesis. The effect is specific to the thyroid gland.

5.2 Pharmacokinetic properties

Vitamin A is readily absorbed from the normal gastrointestinal tract. Less than 5% of circulating vitamin A is bound to lipoproteins in blood in normal condition, but may be up to 65% when hepatic stores are saturated because of excessive intake. When released from liver, vitamin A is bound to retinol-binding protein (RBP). Most vitamin A circulates in the form of retinol bound to RBP. Retinol is conjugated with glucuronic acid; the B-glucuronide undergoes enterohepatic circulation and oxidation to retinol and retinoic acid. Retinoic acid undergoes decarboxylation and conjugation with glucuronic acid.

The pharmacokinetics of Cholecalciferol have been widely studied and are well-known. Cholecalciferol from nutritional sources is almost completely absorbed from within the gastro-intestinal tract in the presence of dietary lipids and bile acids. Cholecalciferol is stored in fat cells and its biological half-life is approximately 50 days.

Cholecalciferol is metabolised by microsomal hydroxylase to form 25-hydroxycolecalciferol (25(OH)D_3, calcidiol), the primary storage form of vitamin D_3. 25(OH)D_3 undergoes a secondary hydroxylation within the kidney to form the predominant active metabolite 1,25-hydroxycholecalciferol (1,25(OH)$_2D_3$, calcitriol). The metabolites circulate in the blood bound to a specific α -globin.

After a single oral dose of Colecalciferol, the maximum serum concentrations of the primary storage form are reached after approximately 7 days. 25(OH)D_3 is then slowly eliminated with an apparent half-life in serum of about 50 days. Cholecalciferol and its metabolites are excreted mainly in the bile and faeces.

After high doses of Cholecalciferol, serum concentrations of 25(OH)D_3 may be increased for months. Overdose-induced hypercalcaemia may persist for weeks.

It is generally believed that alpha-tocopherol succinate is ultimately de-esterified or cleaved to provide alpha-tocopherol once administered to the human body. It is consequently expected that pharmacodynamics and pharmacokinetics similar to that of alpha-tocopherol to be followed.

50 to 80% absorbed is from gastrointestinal tract.

Ascorbic acid is rapidly absorbed by sodium-dependent active transport from the intestine, although the proportion absorbed decrease with increasing doses.
It is present in plasma and is extensively distributed to all cells of the body, with higher levels found in the adrenal glands, pituitary and retina, and lower levels in kidney and muscle tissue. Tissue vitamin C concentrations are higher than that of plasma but saturate before.
Ascorbic acid is readily oxidized to dehydroascorbic acid. Irreversible breakdown yields 2,3-diketogulonic acid (without biological action), which is then oxidised to oxalic and threonic acids.
The main route of excretion of ascorbic acid is in urine, but a small percentage is excreted in the faeces. Absorbed excess doses are largely excreted unchanged in urine. The plasma half-life of ascorbic acid in humans is 16 days.

All the B Vitamins are water soluble vitamins. Quantities in excess of the bodies requirements are excreted either unchanged or as metabolites, mainly in the urine but to a lesser extent also in the faeces.

Small amounts of thiamine are well absorbed from the gastrointestinal tract after oral doses, but the absorption of doses larger than about 5mg is limited. Thiamine is not stored to any appreciable extent in the body and amounts in excess of the body's requirements are excreted in the urine unchanged or as metabolites.
Riboflavin is readily absorbed from the gastrointestinal tract. Although riboflavin is widely distributed to body tissues little is stored in the body.
Riboflavin also crosses the placenta and is distributed into breast milk. It is widely distributed to most body tissues and appears in breast milk.
Riboflavin is excreted in urine, partly as metabolites.
Pyridoxine B_6 (pyridoxal and pyridoxamine) are readily absorbed from the gastrointestinal tract after oral doses and are converted to the active forms pyridoxal phosphate and pyridoxamine phosphate.
Pyridoxine is stored mainly in the liver where there is oxidation to 4-pyridoxic acid. Pyridoxal crosses the placenta and is distributed into breast milk.
As the dose increases, proportionally greater amounts are excreted unchanged in the urine.
Vitamin B_{12} substances bind to intrinsic factor; glycoproteins secreted by the gastric mucosa and are then actively absorbed from the gastrointestinal tract. Absorption is impaired in patients with an absence of intrinsic factor.
Vitamin B_{12} is stored in the liver, excreted in the bile and most of it in the first 8 hours; urinary excretion, however, accounts for only a small fraction in the reduction of total body stores acquired by dietary means. Vitamin B_{12} diffuses across the placenta and also appears in breast milk.
Vitamin B_{12} undergoes extensive enterohepatic recycling; part of a dose is excreted in the urine.

Folic acid given therapeutically enters the portal circulation largely unchanged, since it is a poor substrate for reduction by dihydrofolate reductase. It is converted to the metabolically active form 5 methltetrahydrofolate in the plasma and liver.
The principal storage site of folate is the liver; it is also actively concentrated in the cerebrospinal fluid. Folate undergoes enterohepatic circulation.
Folate is distributed into breast milk. Folic acid is removed haemodialysis.
Folate metabolites are eliminated in the urine and folate in excess of body requirements is excreted unchanged in the urine.

Absorption of zinc from the gastrointestinal tract is incomplete and is reduced in the presence of some dietary constituents such as phytates. Bioavailability of dietary zinc varies widely between different sources, but is about 20 to 30%In the acid conditions of the gastric contents, ferrous fumarate is dissociated and ferrous ions are liberated. These ions are absorbed in the proximal portion of the duodenum.

The ferrous iron absorbed by the mucosal cells of the duodenum is oxidised to the ferric form, and this is bound to protein to form Ferritin.

Ferritin in the mucosal cells releases iron into the blood, where it is bound to transferrin and passed into the iron stores - liver, spleen, and bone marrow.

These stores are a reserve of iron for synthesis of haemoglobin, myoglobin, and iron containing enzymes.

Iron is lost from the body through loss of cells in urine, faeces, hair, skin, sputum, nails, and mucosal cells, and through blood loss.

Ferrous fumarate has the same pattern of absorption and excretion as dietary iron.

Zinc is distributed throughout the body with the highest concentrations found in muscle, bone, skin, eye and prostatic fluids. It is primarily excreted in the faeces and regulation of faecal losses is important in zinc homoeostasis. Small amounts are lost in urine and perspiration.
Copper absorption varies inversely with intake. Absorption range is 12-65%. Copper appears to be eliminated primarily through bile.

In the blood, selenite is mainly absorbed by erythrocytes and enzymatically reduced to hydrogen selenide. Hydrogen selenide serves as the central selenium pool for excretion and for specific incorporation in selenoproteins. In this reduced form, selenium is bound to plasma proteins present in the liver and other organs. The plasmatic secondary transport from the liver to the glutathionperoxidase-synthesing target tissues takes place in the form of selenocystein (selenoprotein P). The further metabolic process of the selenoprotein biosynthesis is currently known only in prokaryotes. Selenocystein is then specifically incorporated into the peptide chains of the glutathionperoxidase.

Excess of hydrogen selenide is transformed into methylated metabolites (methyl selenol, dimethylselenide and trimethylselenonium ion) prior to being excreted into urine and/or exhaled.

The total quantity of selenium in the human body is between 3 mg and 20 mg. In human, selenium is excreted in feces, urine or lung, depending on the administered dosage. Selenium is primarily renally excreted in the form of trimethylselenonium ion. The excretion depends on the selenium status.

The selenium excretion after the intravenous or oral intake takes place in three phases with a terminal half-life of 65 to 116 days.

Iodine is quickly absorbed, mainly in the small intestine. Once absorbed is rapidly distributed across the extracellular fluid. Then it will be captured by thyroid cells as a substrate for thyroid hormones. Only 30 percent of the body's iodine is concentrated in the thyroid tissue and thyroid hormones. The remaining nonhormonal iodine is found in a variety of tissues, including mammary tissue, eye, gastric mucosa, cervix, and salivary glands. Iodine crosses the placental barrier and is secreted in breast milk.. The main elimination is urinary and, lesser amount, faecal.

5.3 Preclinical safety data

None stated

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Methyl paraben, propyl paraben, microcrystalline cellulose, purified talc, carmoisine red, isopropyl alcohol, methylene dichloride.

BP: British Pharmacopoeia

6.2 Incompatibilities

None known

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store between 4°C and 25°C. Protect from light.

6.5 Nature and contents of container

PVC blisters and aluminium foil.

6.6 Special precautions for disposal of used medicinal product or waste materials derived from such medicinal product and other handling of the product

None stated

7. APPLICANT/HOLDER OF CERTIFICATE OF PRODUCT REGISTRATION

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9. NAFDAC REGISTRATION NUMBER(S):

Not available