1. NAME OF THE MEDICINAL PRODUCT
Avromult Syrup

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Each 10ml contains:

L-Lysine 100mg
Vitamin A 1000i.u
Vitamin C 50mg
Vitamin D 200i.u
Nicotinamide 10mg
Vitamin B1 1.5mg
Vitamin B2 1.5mg
Vitamin B6 2mg
Vitamin B12 1mcg
Calcium Pantothenate 12mg

For full list of excipients, see section 6.1.

3. Pharmaceutical form
Oral Syrup

4. CLINICAL PARTICULARS
4.1 Therapeutic indications
- Deficiency states
- Healthy growth in children and adolescents
- Recovery from illness, infections, injury, burns and surgery
- Anorexia (loss of appetite)
- Nutritional supplement in cases of inadequate dietary intake

4.2 Posology and method of administration
Posology
Infants and Children 1 – 5 years: 7.5ml per day
Adolescents and Adults: 15ml per day

Method of administration
For oral administration.

4.3 Contraindications
- Cases of known hypersensitivity to any of the ingredients
- Stomach ulcers or other intestinal diseases.
- Patients with history of impairment of amino acid or vitamin absorption and amino acid or vitamin metabolic disorders
- Use with caution in patients with renal impairment
- Concurrent administration of other vitamin A or vitamin D-containing products

4.4 Special warnings and precautions for use
When prescribing Avromult Syrup, as with all multi-vitamin preparations, allowance should be made for vitamins obtained from other sources.
While children are taking Avromult Syrup no other vitamin supplement containing vitamins A and D should be taken unless under medical supervision.
Excessive dosage of vitamin A and D may lead to hypervitaminoses. Due allowance should always be made for intake of these vitamins from other sources.

4.5 Interaction with other medicinal products and other forms of interaction

VITAMIN A
Cholestyramine and mineral oil reduce the absorption of vitamins A,D and E. Avoid prolonged use.
Large doses of vitamin A may increase the hypoprothrombic effect of warfarin.
Oral contraceptive use may increase plasma levels of vitamin A.

VITAMIN B_6 (PYRIDOXINE)
Pyridoxine antagonizes the therapeutic action of levodopa by facilitating the transformation of levodopa into dopamine before levodopa can cross the blood-brain-barrier and enter the CNS.

VITAMIN B_{12} (CYANOCOBALAMIN)
Neomycin may impair absorption of vitamin B_{12}.

VITAMIN C
Administration of vitamin concurrently with sulphonamides hinders solubility of sulphonamides increasing the risk of crystalluria.
Acidification of the urine by vitamin C causes reabsorption of acidic drugs from the tubules, resulting in higher, more prolonged levels.
The effect of basic drugs such as amphetamines and tricyclic antidepressants may be reduced by vitamin C.
Vitamin C may increase the serum levels of oestrogens and reduce the anticoagulant effect of warfarin.

VITAMIN D
Phosphates from phosphate-containing drugs or magnesium-containing antacids may lower calcium levels and contribute to vitamin D deficiency.
Phenytoin or barbiturates may decrease the half-life of vitamin D

4.6 Fertility, pregnancy and lactation
Not indicated.

4.7 Effects on ability to drive and use machines
None stated.

4.8 Undesirable effects
Vitamin A
Adverse effects are extremely rare at daily doses of less than 9 mg (16363.6 IU).

Ergocalciferol (Vitamin D_2)
The only known adverse effects of vitamin D occur when excessive doses are taken. Adverse effects are not anticipated at the quantity present in Avromult Syrup.

Ascorbic Acid (C), Nicotinamide, Pyridoxine (B_6), Riboflavin (B_2) & Thiamine (B_1)
These water soluble vitamins are generally non-toxic compounds with a wide margin of safety, the excess amounts being rapidly excreted in the urine. Adverse effects are not anticipated at the quantities present in Avromult Syrup.

4.9 Overdose
Symptoms and signs
Avromult Syrup contains levels of vitamins which present little risk in overdose.

Vitamin A
Acute administration of high doses of vitamin A can cause headache, nausea, vomiting and irritability. In infants acute toxicity can lead to transient hydrocephalus. All these effects disappear within 24 hours of taking retinol.

Ergocalciferol (Vitamin D_2)
Excessive doses of vitamin D, 60 000 units per day, can result in hypercalcaemia and hypercalciuria. Adverse effects of hypercalcaemia may include muscle weakness, apathy, headache, anorexia, nausea and vomiting, hypertension and cardiac arrhythmias.

Thiamine hydrochloride (Vitamin B_1)
When taken orally, thiamine is non-toxic. If large doses are ingested they are not stored by the body but excreted unchanged by the kidneys.

Riboflavin (Vitamin B_2)
Riboflavin has been found to be practically non-toxic.

Pyridoxine hydrochloride (Vitamin B_6)
Acute doses less than 500mg per day appear to be safe. Excessive doses may lower serum folate concentrations. Sensory neuropathy has been described with chronic dosing of 200 mg daily.

Nicotinamide
A single large overdose of nicotinamide is unlikely to have serious ill effects, though transient abnormalities of liver function might occur.

Ascorbic acid (Vitamin C)
Ascorbic acid is not stored to a great extent by the body; any excess amounts are eliminated in the urine. Ascorbic acid is thought to become toxic at chronic doses in excess of 6 g.

Treatment
Treatment should be supportive and symptomatic.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Amino Acid, Multivitamin and Mineral, oral preparations.

ATC code: A11AA02

<u>L-Lysine Hydrochloride</u>
L-Lysine Hydrochloride is an aliphatic amino acid that is an essential constituent of the diet. It is used as a dietary supplement.

<u>Vitamin A</u>
Vitamin A, a fat-soluble vitamin, is essential for growth, for the development and maintenance of epithelial tissue, and for vision, particularly in dim light. Vitamin A deficiency develops when the dietary intake is inadequate. Prolonged deficiency leads to xeropthalmia or 'dry eye' the initial symptoms of which is night blindness, which may progress to severe eye lesion and blindness. Other symptoms include changes in the skin and mucous membranes.
Vitamin A has also been used alone to treat various skin disorders including acne and Psoriasis.

<u>Vitamin B1 (Thiamine)</u>
Thiamine is practically devoid of pharmacodynamic actions when given in usual therapeutic doses; even large doses produce no discernible effects. Isolated clinical reports of toxic reaction to the long-term parenteral administration of Thiamine probably represent rare instances of hypersensitivity.
The only established therapeutic use of Thiamine is in the treatment or the prophylaxis of Thiamine deficiency. The syndromes of Thiamine deficiency seen clinically can range from beriberi through wernicke's encephalopathy and korsakoff's syndrome to alcoholic polyneuropathy. Thiamine, a water-soluble vitamin, is an essential coenzyme for carbohydrate metabolism. Thiamine deficiency develops when the dietary intake is inadequate; severe deficiency leads to chronic beriberi characterized by peripheral neuritis, bradycardia, muscle weakness and paralysis.

Vitamin B2 (Riboflavin)
Riboflavine, a water-soluble vitamin, is essential for the utilization of energy from food. The active, phosphorylated forms, flavine mononucleotide and flavine adenine dinucleotide are involved as coenzymes in oxidative/reductive metabolic reactions.
Riboflavine deficiency develops when the dietary intake is inadequate. Deficiency leads to the development of a well-defined syndrome known as ariboflavinosis, characterized by cheilosis, angular stomatitis, glossitis and seborrhoeic keratosis of the nose and ano-genital region. There may be ocular symptoms including itching and burning of the eyes, photophobia and corneal vascularisation. Riboflavine deficiency may occur in association with other vitamin B complex deficiency states such as pellagra.
Riboflavine is used in the treatment and prevention of Riboflavine deficiency.

Vitamin B6 (Pyridoxine)
Pyridoxine, a water–soluble vitamin is involved principally in amino acid metabolism, but is also involved in carbohydrate and fat metabolism. It is also required for the formation of haemoglobin.
Deficiency of Pyridoxine is rare in humans due to its wide spread distribution in foods. Pyridoxine deficiency may however be drug induced and can occur, for instance, during isoniazid therapy. Inadequate Pyridoxine deficiency in adults lead to the development of peripheral neuritis, deficiency in children also affect the CNS.
Pyridoxine is used in the treatment and prevention of Pyridoxine deficiency states. Pyridoxine has also been used to treat seizure due to hereditary syndromes of Pyridoxine deficiency or dependency in infants.
Pyridoxine has also been tried in a wide variety of other disorders, including the treatment of depression and other symptoms associated with the premenstrual syndrome and the use of oral contraceptives.

Vitamin B12 (Cyanocobalamin)
Vitamin B12, water-soluble vitamins occur in the body mainly as methylcobalamin and as adenosylcobalamin and hydroxycobalamin. It act as coenzyme in nucleic acid synthesis.
Vitamin B12 deficiency may occur in strict vegetarians with an inadequate dietary intake, in patients with malabsorption syndromes or metabolic disorder, nitrous oxide induced megaloblastosis or following anaemias and neurological damage.
Vitamin B12 preparations are used in the treatment and prevention of Vitamin B12 deficiency. It is desirable to identify the cause of deficiency before commencing therapy. Treatment usually results in rapid haematological improvement and a striking clinical response.

Vitamin C (Ascorbic Acid)
Ascorbic acid, a water-soluble vitamin is essential for the synthesis of collagen and intercellular material.
Ascorbic acid deficiency develops when the dietary intake is inadequate. Deficiency leads to the development of a well-defined syndrome known as scurvy characterized by capillary fragility, bleeding (especially from small blood vessel and the gum) anaemia, cartilage and bone lesions and slow healing of wounds.
Ascorbic acid is used in the treatment and prevention of Ascorbic acid deficiency. It completely reverses symptoms of deficiency. Ascorbic acid has been used to acidify urine and has also been tried in the treatment of idiopathic methaemoglobinaemia and many other disorders.

Vitamin D (Cholecalcifrol)
Cholecalciferol is the naturally occurring form of Vitamin D. It is produced from 7-hydrochlolesterol, a sterol present in mammalian skin by ultraviolet irradiation.
Vitamin D compounds are fat-soluble sterols, sometimes considered to be hormones or hormone precursors, which are essential for the proper regulation of calcium and phosphate homeostasis and bone mineralisation.
Vitamin D deficiency develops when there is inadequate exposure to sunlight or lack of the vitamin in the diet. Deficiency takes a long time to develop due slow release of the vitamin from body stores. It may occur in infants who are breast fed without supplemental vitamin D or exposure to sunlight, in the elderly whose mobility and thus exposure to light may be impaired, and in persons with fat malabsorption syndromes; certain disease states such as renal failure may also affect the metabolism of vitamin D substances to metabolically active forms and thus result in deficiency. Deficiency results in osteomalacia in adults. In children, rickets develops.
Vitamin D is uded in the treatment of vitamin D deficiency states and hypocalcaemia in disorders such as hypoparathyroidism and secondary hyper parathyroidism.

Nicotinamide

Nicotinic acid and nicotinamide, the form that occurs naturally in the body are water-soluble vitamin B substances, which are converted to Nicotinanide Adenine Dinucleotide Phosphate (NADP). These coenzymes are involved in electron transfer reactions in the respiratory chain.

Nicotinamide deficiency develops when dietary intake is inadequate. Deficiency leads to the development of a syndrome known as pellagra characterized by skin lesions, especially on areas exposed to sunlight, with hyperpigmentation and hyperkeratinisation. Other symptoms include diarrhoea, abdominal pain, glossitis, stomatitis, and loss of appetite, headache, lethargy and mental and neurological disturbances. Nicotinic acid deficiency may occur in association with other vitamin B complex deficiency states.

Nicotinamide is used in the treatment and prevention of Nicotinic acid deficiency. Nicotinamide is preferred, as it does not cause vasodilatation.

Calcium D-Pantothenate

Pantothenic acid is traditionally considered to be a vitamin B substance. It is a component of co-enzyme A which is essential in the metabolism of carbohydrate, fat and protein.

Deficiency of pantothenic acid is unlikely in man because of its wide spread distribution in food. It is administered as a nutritional supplement often as calcium salt and usually in conjunction with other vitamins of the B group.

Calcium regulates transport of other nutrients into the plant and is also involved in the activation of certain plant enzymes. Calcium deficiency results in stunting.

5.2 Pharmacokinetic properties

L-Lysine

L-Lysine is readily absorbed from the gastrointestinal tract. Excess is discarded, typically in the urine.

Vitamin A

Vitamin A is readily absorbed from the gastro intestinal tract but absorption may be reduced in the presence of fat malabsorption, low protein intake, or impaired liver or pancreatic function. Vitamin A esters are hydrolyzed by pancreatic enzymes to retinol, which is then absorbed. Some retinol are stored in t he liver. It is released from the liver bound to a specific α_1 – globulin (retinol – binding protein) in the blood. The retinol not stored in the liver undergoes glucuronide conjugation and subsequent oxidation to retinal and retinoic acid, these and other metabolites are excreted in urine and faeces. Vitamin A does not readily diffuse across the placenta but is present in the milk of nursing mothers.

Vitamin B_1 (Thiamine)

Thiamine is well absorbed from the gastro intestinal tract following oral administration, although the absorption of large doses is limited. It is also rapidly absorbed following intra muscular administration. It is widely distributed to most body tissues and appears in breast milk. 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 as unchanged Thiamine or as metabolites.

Thiamine requirements are directly related to the carbohydrate intake and the metabolic rate. A daily dietary intake of 1 to 1.3mg of Thiamine is recommended for healthy men and 0.7 to 1mg for healthy women.

Vitamin B_2 (Riboflavin)

Riboflavine is readily absorbed from the gastro intestinal tract. Although Riboflavine is widely distributed to body tissues, little is stored in the body. Riboflavine is converted in the body to the coenzyme Flavine mononucleotide and then to another coenzyme Flavine adenine dinucleotide. About 60% of FMN and FAD are bound to plasma proteins. Riboflavine is excreted in urine, mainly as metabolites. As the dose increases, larger amounts are excreted unchanged. Riboflavine crosses the placenta and is distributed in breast milk.

The Riboflavine requirement is often related to the energy intake but it appears to be more closely related to the resting metabolic requirements. A daily dietary intake of about 1.3 to 1.8mg of Riboflavine is recommended.

Vitamin B_6 (Pyridoxine)

Pyridoxine is readily absorbed from the gastro-intestinal tract following oral administration and is converted to the active forms pyridoxal phosphate and pyridoxamine phosphate. They are stored mainly in the liver where there is oxidation to 4-pyridoxic acid, which is excreted in the urine. Pyridoxine crosses the placenta and also appears in the breast milk.

For adults, the daily requirement of Pyridoxine is probably about 2mg and this amount is present in most normal diets. Meats, especially liver, cereals, eggs, fish and certain vegetables and fruits are good source of Pyridoxine.

Vitamin B_{12} (Cyanocobalamin)

Vitamin B_{12} substances bind to intrinsic factor and are then actively absorbed from the gastro intestinal tract. Absorption is impaired in patients with an absence of intrinsic factor, with a malabsorption syndrome or with disease or abnormality of the gut, or after gastrectomy.

Vitamin B_{12} is extensively bound to specific plasma proteins called Transcobalamins, Transcobalamin II appears to be involved in the rapid transport of the cobalamins to tissues. It is stored in the liver, excreted in the bile and undergoes enterohepatic recycling; part of a dose is excreted in the urine, most of it in the first 8 hours. Vitamin B_{12} diffuses across the placenta and also appears in breast milk.

For adults, the daily requirement of Vitamin B_{12} is probably about 1 to 3µg and this amount is present in most normal diets.

Vitamin C (Ascorbic Acid)

Ascorbic acid is readily absorbed from the gastro intestinal tract and is widely distributed in the body tissues. It is reported to be 25% bound to plasma proteins. The amount of ascorbic acid in the body in health is about 1.5g. The concentration is higher in leucocytes and platelets than in erythrocytes and plasma. In deficiency states the concentration in leucocytes declines later and at a slower rate, and has been considered to be a better criterion for the evaluation of deficiency than the concentration in plasma.

Ascorbic acid is reversibly oxidised to dehydroascorbic acid; some is metabolised to ascorbate – 2 – sulphate, which is inactive and oxalic acid, which are excreted in the urine. Ascorbic acid in excess of the body's needs is also rapidly eliminated in the urine. Ascorbic acid crosses the placenta and is distributed into breast milk. It is removed by haemodialysis.

A daily dietary intake of about 30 to 60mg Ascorbic acid has been recommended for adults. There is, however, wide variation in individual requirements. Humans are unable to form their own ascorbic acid and so a dietary source is necessary. Most dietary ascorbic acid is obtained from fruit and vegetable sources; only small amounts are present in milk and animal tissues.

Vitamin D (Cholecalcifrol)

Vitamin D Substances Are Well Absorbed From The Gastrointestinal Tract. The Presence Of Bile Is Essential For Adequate Intestinal Absorption; Absorption May Be Decreased In Patients With Decreased Fat Absorption.

Vitamin D And Its Metabolites Circulate In The Blood Bound To A Specific A-Globulin. Vitamin D Can Be Stored In Adipose And Muscle Tissues For Long Periods Of Time. It Is Slowly Released From Such Storage Sites And From The Skin Where It Is Formed In The Presence Of Sunlight Or Ultraviolet Light. Ergocalciferol And Cholecalciferol Have A Slow Onset And A Long Duration Of Action.

Cholecalciferol And Ergocalciferol Are Hydroxylated In The Liver By The Enzyme Vitamin D 25-Hydroxylase To Form 25-Hydroxycholecalciferol (Calcifediol) And 25- Hydroxyergocalciferol Respectively. These Compounds Undergo Further Hydroxylation In The Kidneys, Including The Formation Of The 1,24,25-Trihydroxy Derivatives. Of The Synthetic Analogues, Alfacalcidol Is Converted Rapidly In The Liver To Calcitriol, And Dihydrotachysterol Is Hydroxylated, Also In The Liver, To Its Active Form 25-Hydroxydihydrotachysterol.

Vitamin D Compounds And Their Metabolites Are Excreted Mainly In The Bile And Faeces With Only Small Amounts Appearing In The Urine; There Is Some Enterohepatic Recycling But It Is Considered To Have A Negligible Contribution To Vitamin D Status. Certain Vitamin D Substances May Be Distributed Into Breast Milk.

Nicotinamide

Nicotinamide is absorbed readily from all portions of the intestinal tract and the vitamin is distributed to all tissues. The principal route of metabolism of Nicotinic acid and nicotinamide is by the formation of N—

methylnicotinamide, which in turn is metabolized further. Smmall amounts of the unchanged vitamins appear in the urine following therapeutic doses of nicotinic acid and nicotinamide.
The daily adult requirement is probably about 15-20mg.

Calcium Panthothenate

Pantothenic acid is readily absorbed from the gastro intestinal tract following oral administration. It is widely distributed in the body tissues and appears in breast milk. About 70% of Pantothenic acid is excreted unchanged in the urine and about 30% in the fences.
Pantothenic acid is rapidly absorbed in foods-meat, legumes and whole grain cereals are particularly rich sources. Recommended daily intakes of Pantothenic acid have not been set, but human requirements are adequately met by a daily intake of about 4 to 10mg.

5.3 Preclinical safety data
No further data

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Methyl Hydroxybenzoate
Propyl Hydroxybenzoate
Sucrose
Orange Flavour
Polysorbate 80
Glycerol
Xanthan Gum
Deionised Water

6.2 Incompatibilities
Not applicable.

6.3 Shelf Life
3 years

6.4 Special precautions for storage
Store below 30°C. Protect from light.

6.5 Nature and contents of container
100ml Amber bottle with aluminium screw cap.

6.6 Special precautions for disposal and other handling
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. APPLICANT/MANUFACTURER
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