

1. NAME OF THE MEDICINAL PRODUCT

Forceval Capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains:

Vitamin A (as β -Carotene)	HSE	2,500.0 iu
Vitamin D2 (Ergocalciferol)	HSE	400.0 iu
Vitamin B1 (Thiamine)	PhEur	1.2 mg
Vitamin B2 (Riboflavin)	PhEur	1.6 mg
Vitamin B6 (Pyridoxine)	PhEur	2.0 mg
Vitamin B12 (Cyanocobalamin)	HSE	3.0 mcg
Vitamin C (Ascorbic Acid)	PhEur	60.0 mg
Vitamin E (dl- α -Tocopheryl Acetate)	USP	10.0 mg
d-Biotin (Vitamin H)	FCC	100.0 mcg
Nicotinamide (Vitamin B3)	PhEur	18.0 mg
Pantothenic Acid (Vitamin B5)	PhEur	4.0 mg
Folic Acid (Vitamin B Complex)	PhEur	400.0 mcg
Calcium	USP	100.0 mg
Iron	PhEur	12.0 mg
Copper	PhEur	2.0 mg
Phosphorus	USP	77.0 mg
Magnesium	PhEur	30.0 mg
Potassium	BPC	4.0 mg
Zinc	USP	15.0 mg
Iodine	PhEur	140.0 mcg
Manganese	USP	3.0 mg
Selenium	HSE	50.0 mcg
Chromium	HSE	200.0 mcg
Molybdenum	PhEur	250.0 mcg

3. PHARMACEUTICAL FORM

Brown and maroon, oblong, soft gelatin capsule printed with **FORCEVAL** in white on one side and with **6377** in white on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

1. 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.
2. 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.
3. As a therapeutic nutritional adjunct in convalescence from illness, e.g. where anorexia or cachexia exists and following chemo- or radio-therapy.
4. As a therapeutic nutritional adjunct in convalescence from surgery, e.g. where nutritional intake continues to be inadequate.
5. 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.
6. As a therapeutic nutritional adjunct where food intolerance exists, e.g. exclusion diets.
7. As an adjunct in synthetic diets, e.g. in phenylketonuria, galactosaemia and ketogenic diets.

4.2 Posology and method of administration

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

Forceval Capsules are not recommended for this age group.

4.3 Contraindications

Hypercalcaemia, haemochromatosis and other iron storage disorders.

4.4 Special warnings and special precautions for use

Whilst taking Forceval 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 Forceval 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 E123 (amaranth) 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 Forceval Capsules, which contain 4.5mg per recommended daily dose, before use.

Patients with thyroid disorders should seek medical advice before taking Forceval 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 sulphate reduce the absorption of tetracyclines.

4.6 Pregnancy and lactation

Forceval 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

Undesirable effects are listed by MedDRA System Organ Classes.

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

Very common: $\geq 1/10$

Common: $\geq 1/100$ to $< 1/10$

Uncommon: $\geq 1/1,000$ to $< 1/100$

Rare: $\geq 1/10,000$ to $< 1/1,000$

Very rare: $< 1/10,000$

Not known: cannot be estimated from the available data

Immune system disorders	<i>Not known:</i> Hypersensitivity reaction (such as rash)
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Gastrointestinal disorders	<p><i>Not known:</i></p> <p>Gastrointestinal disturbances (such as nausea, vomiting and abdominal pain)</p>
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4.9 Overdose

No cases of overdosage due to Forceval therapy have been reported. Any symptoms which may be observed due to the ingestion of large quantities of Forceval 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 ($>142 \mu\text{mol/l}$) 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.
7. Any fluid or electrolyte imbalance should be corrected.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

The following account summarises the pharmacological effects of the vitamins and minerals in Forceval 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 gastrointestinal 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 B₁ (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, gastrointestinal disturbances, tachycardia, irritability and neurological symptoms. Gross deficiency of thiamine (and other Vitamin B group factors) leads to the condition beri-beri.

Vitamin B₂ (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 B₆ (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 B₁₂ (Cyanocobalamin)

Vitamin B₁₂ 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 B₁₂ interferes with haemopoiesis and produces megaloblastic anaemia.

Vitamin C (Ascorbic Acid)

Vitamin C cannot be synthesised by man therefore a dietary source is necessary. It acts as a cofactor in numerous biological processes including the hydroxylation of proline to hydroxyproline. In deficiency, the formation of collagen is, therefore, impaired. Ascorbic acid is important in the hydroxylation of dopamine to noradrenaline and in hydroxylations occurring in steroid synthesis in the adrenals. It is a reducing agent in tyrosine metabolism and by acting as an electron donor in the conversion of folic acid to tetrahydrofolic acid is indirectly involved in the synthesis of purine and thymine. Vitamin C is also necessary for the incorporation of iron into ferritin. Vitamin C increases the phagocytic function of leucocytes; it possesses anti-inflammatory activity and it promotes wound healing. Deficiency can produce scurvy. Features include swollen inflamed gums, petechial haemorrhages and subcutaneous bruising. The deficiency of collagen leads to development of thin watery ground substances in which blood vessels are insecurely fixed and readily ruptured. The supportive components of bone and cartilage are also deficient causing bones to fracture easily and teeth to become loose. Anaemia commonly occurs probably due to Vitamin C's role in iron metabolism.

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 (Dicalcium 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 (Dicalcium 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.

Pantothenic Acid

Pantothenic acid is incorporated into co-enzyme A and is involved in metabolic pathways involving acetylation which includes detoxification of drug molecules and biosynthesis of cholesterol, steroid hormones, mucopolysaccharides and acetylcholine. CoA has an essential function in lipid metabolism.

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.

Vitamin H (d-Biotin)

Biotin is a co-enzyme for carboxylation during the metabolism of proteins and carbohydrates.

Selenium

Selenium is an essential trace element, deficiency of which has been reported in man. It is thought to be involved in the functioning of membranes and the synthesis of amino acids. Deficiency of selenium in the diet of experimental animals produces fatty liver followed by necrosis.

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 Sulphate)

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 Sulphate)

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 Sulphate)

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 Sulphate)

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.

Chromium (Chromium Amino Acid Chelate 10%)

Chromium is an essential trace element involved in carbohydrate metabolism.

Molybdenum (Sodium Molybdate)

Molybdenum is an essential trace element although there have been no reports of deficiency states in man. Molybdenum salts have been used to treat copper poisoning in sheep.

5.2 Pharmacokinetic properties

The following account describes the absorption and fate of each of the active constituents of Forceval Capsules.

Vitamin A

Except when liver function is impaired, Vitamin A is readily absorbed. β -carotene (as in Forceval 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 B₁ (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 B₂ (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 B₆ (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 B₁₂ (Cyanocobalamin)

Cyanocobalamin is absorbed from the gastro-intestinal tract and is extensively bound to specific plasma proteins. A study with labelled Vitamin B₁₂ 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 C (Ascorbic Acid)

Ascorbic acid is readily absorbed from the gastro-intestinal tract and is widely distributed in the body tissues. Ascorbic acid in excess of the body's needs is rapidly eliminated in the urine and this elimination is usually accompanied by a mild diuresis.

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 (Dicalcium Phosphate)

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

Phosphorus (Dicalcium 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.

Calcium Pantothenate

Pantothenic acid is readily absorbed from the gastro-intestinal tract and is widely distributed in the body tissues. About 70% of pantothenic acid is excreted unchanged in the urine and about 30% in the faeces.

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.

Vitamin H (d-Biotin)

Following absorption, biotin is stored in the liver, kidney and pancreas.

Selenium

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

Ferrous Fumarate (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 fumarate. In conditions of iron deficiency, absorption is increased and, conversely, it is decreased in iron overload. Iron is stored as ferritin.

Copper Sulphate (Copper)

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

Magnesium Oxide (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 Sulphate (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 Sulphate (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 Sulphate (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.

Chromium Amino Acid Chelate 10% (Chromium)

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

Sodium Molybdate (Molybdenum)

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

5.3 Preclinical safety data

There are no pre-clinical data of relevance to the prescriber which are additional to that already included in other sections of the SPC.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Soya Bean Oil	BP
Soya Lecithin	HSE
Hard Vegetable Fat (Biscuitine 621)	HSE
Yellow Beeswax	PhEur
Purified Water	PhEur
Gelatin	PhEur
Glycerine	PhEur
Ponceau 4R (E124)	HSE
Amaranth (E123)	HSE
Titanium Dioxide (E171)	PhEur
Red Iron Oxide Paste (E172)	HSE
Vegetable Black Paste (E153)	HSE

6.2 Incompatibilities

No major incompatibilities are known.

6.3 Shelf life

24 months, as packaged for sale.

6.4 Special precautions for storage

Store in a cool dry place at a temperature not exceeding 25°C.
Protect from light.

6.5 Nature and contents of container

The product is presented in press-thru blister packs, each blister strip containing 15 Forceval capsules. The blister strip is composed of PVC/PVdC with a printed aluminium foil lidding. The foil is printed (red on gold) with the name and PL number of the product, the number of vitamins and minerals per capsule and the daily dose.

The product is available in packs of 30, 90 or 600 capsules.

6.6 Instructions for use and handling

Not applicable.

7. MARKETING AUTHORISATION HOLDER

Alliance Pharmaceuticals Limited
Avonbridge House
Bath Road
Chippenham
Wiltshire
SN15 2BB
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

MA 200/00305

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

1st February 2006

10. DATE OF REVISION OF THE TEXT

October 2013