For the use only of a Registered Medical Practitioner or a Hospital or a Laboratory

MEGASHELCAL
(Combipack of fish lipid oil capsules and calcium with vitamin D_3 & minerals tablets)

COMPOSITION
Each combi pack contains:

Formula A: Fish Lipid Oil Capsules

Each soft gelatin capsule contains:
Omega-3-Marine Triglycerides B.P. ……. 700 mg
(Providing Eicosapentaenoic Acid 70 mg and Docosahexaenoic Acid 280 mg)
Approved colours used in capsule shells.

Formula B: Calcium with Vitamin D_3 & Minerals Tablets

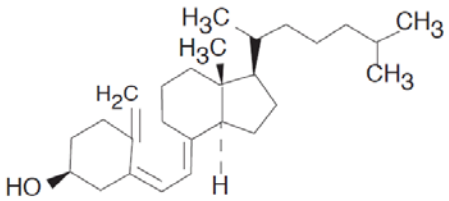
Each film-coated tablet contains:
1250 mg Calcium Carbonate from an organic source (Powdered Oyster Shell) equivalent to
Elemental Calcium ……. 500 mg
Vitamin D_3 I.P. …… 250 IU
Magnesium (Elemental) …….. 40 mg As Heavy Magnesium Oxide I.P.
Manganese (Elemental) ……. 1.8 mg As Manganese Sulfate (as Monohydrate) U.S.P.
Zinc (Elemental) ……..... 7.5 mg As Zinc Sulphate Monohydrate I.P.
Copper (Elemental) ……..... 1.0 mg As Cupric Sulfate U.S.P.
Boron (Elemental) ……..… 250 mcg As Sodium Borate B.P.
Colours: Lake of Brilliant Blue FCF, Titanium Dioxide I.P. and Titanium Dioxide coated Mica Pearlescent Pigments.
Appropriate overages of vitamin added to compensate for loss on storage.

DESCRIPTION
During pregnancy the developing fetus for its rapid growth of cells and tissues require nutrition. But for its nutritional requirement is dependent solely on the mother. Nutritional status of the mother decides the outcome of pregnancy. A number of complications of pregnancy are associated with sub optimal nutritional status of various vitamins and minerals. There is an increased need of various nutrients during pregnancy. WHO and other medical institutions have recommended dietary allowances during pregnancy for various vitamins and minerals. Some of the important ones are as follows: Calcium 1000-1200 mg Zinc 15 mg Vitamin D 10 g Recent studies have also confirmed the role of EFAs during pregnancy. Omega 3 fatty acids and calcium are essential supplements for overall development of fetus and mother. Last trimester of pregnancy is a critical period for accumulation of DHA in brain and retina of fetus. DHA plays crucial role in growth and development of central nervous system and visual function in infants. Omega 3 fatty acids, Calcium, Zinc, are effective in prevention of pre eclampsia, PIH, pre term labor and low birth weight infants. Omega 3 fatty acids and Zinc help in reducing chances of post-Partum depression. In the first six months of infancy baby is solely dependent on mother's milk as source of nutrition. All the micronutrients along with fatty acids are secreted in mother's milk so it is advisable to improve nutritional status of mother during nursing. Studies have shown that babies receiving increased amounts of Omega 3 fatty acids have better IQ. All these

advantages make it prudent to supplement Megashelcal from 2nd trimester of pregnancy right through lactation.

Vitamin D3 (Cholecalciferol)

Cholecalciferol is the naturally occurring form of Vitamin D_3. It is produced from 7-dehydro cholesterol, a sterol present in mammalian skin, by ultraviolet irradiation. It's empirical formula is $C_{27}H_{44}O$, and molecular weight is 384.6. It is chemically as (5Z,7E)-(3S)-9,10- secocholesta-5,7,10(19)-triene-3-ol.



Calcium

Calcium is a mineral that is present naturally in the food. It is necessary for many normal functions of body mainly, bone formation and maintenance.

CLINICAL PHARMACOLOGY

PHARMACODYNAMIC

A fish lipid concentrates with a high content of the essential polyunsaturated fatty acids (PUFA) of the ω3 series, namely eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA).

A regular intake of the concentrate in diet leads to a sustained reduction in plasma triglyceride levels following which the values remain on a plateau with continued use or return within two or three months to previous levels if the concentrate is discontinued.

The PUFA are incorporated into the normal lipid metabolism but are not identifiable to any extent in depot fat. The mechanism of effect appears to be via inhibition of triglyceride synthesis.

Calcium is the major constituent found in the various part of the body. e.g. bone, teeth etc. Calcium carbonate plays a critical role in the formation of bon, in chronic renal failure patients; calcium carbonate is used as a phosphate binding agent. Calcium carbonate has three main actions: it neuterlizes gastric acid, supplements dietary calcium and sequesters phosphorus in the intestine.

Vitamin D_3 is cholecalciferol , the naturally occurring form of vitamin D. After absorption, it is rapidly hydroxylated to calcitriol, active form of vitamin D. It enhances the absorption of calcium hence it is commonly prescribed along with various bones diseases or as nutritional supplement during adolescents and pregnancy and lactation.

Minerals and trace elements other than calcium are involved in skeletal growth,

Magnesium: Magnesium is involved in bone and mineral homeostasis and is important in bone crystals growth and stabilization. Magnesium is a cofactor in more than 300 enzymatic reactions and plays a major role in bone cell function and hydroxyapatite crystallization and growth.

Manganese: It is cofactor for several enzymes, it assist bone formation and pyruvate conversion.

Zinc: It is cofactor for several enzymes. It is essential for synthesis of nucleic acid, protein metabolism and cell membrane. It also play role in wound healing, immune function, growth, development of sexual organs and bones, insulin function, it is component of superoxide dismutase.

Copper: It is an essential component of the enzymatic systems involved in bone matrix turnover. Copper improves synthesis of collagen which is an important component of connective tissues.

Boron: Boron play role in skeletal growth and may have key role in brain activities.

PHARMACOKINETICS

The absorption of Omega-3-Marine Triglycerides is similar to that of other dietary lipids, i.e. mainly from the upper part of the small intestine and it is distributed into plasma fatty acids and blood cell lipids. The total plasma glyceride levels of EPA and DHA increase from a pre-treatment level of 0.5 % to a peak of 30 % and 15 % at 12 days respectively, falling then to plateau levels of 23 % and 18 % after 16 days.

There is a corresponding decrease in the level of ω6 fatty acids in free and bound form as plasma triglycerides. EPA and DHA are widely distributed following absorption from the gut and the effect has been quantified in weanling and adult rats.

The proportion of 20:5 ω3 in heart, retina and brain, suggest that these tissues have a low affinity for this fatty acid. DHA accumulated in all tissues except adipose tissue and to a lesser extent in platelets. DHA has a high affinity for retina, brain and heart lipids.

After oral administration Calcium, vitamin D3 and mineral were well absorbed from the intestine, utilized for various biochemical reactions and are excreted out in urine, sweat, faeces and bile.

Calcium Carbonate: Calcium Carbonate is well absorbed from the GI tract in the presence of gastric acid where it is converted to calcium chloride. Calcium carbonate is absorbed as free calcium and bicarbonate ions. Approximately half the calcium in serum is protein bound 5-10% complexed in the form of small readily diffusible organic salts and the remainder as free ions.

Vitamin D_3: Vitamin D_3 which is completely absorbed from the small intestine enhances the absorption of calcium.

Magnesium: The efficacy of magnesium absorption varies widely from 35% to 45%. Magnesium may be absorbed along the length of the small intestine, but most absorption

occurred in the jejunum. The efficacy of the absorption varies with the magnesium in the diet, and the constipation of the diet as whole.

Manganese: Manganese is absorbed throughout the small intestine. Manganese is transported bound to a macroglobulin, transferrin and transmanganin.

Zinc: The absorption of zinc is by two pathways similar to those of calcium. A saturable carrier mechanism involving para-cellular movement at high zinc intakes. Zinc absorption is affected by the level of zinc in the diet and presence of interfering substances especially phytates.

Copper: It is absorbed after oral administration from GIT. It is an essential component of the enzymatic systems involved in bone matrix turnover.

Boron: It is a ultra- trace element obtained from food as sodium borate. Boron is rapidly and almost completely absorbed.

INDICATIONS

Megashelcal is indicated from the 2nd trimester of pregnancy right through lactation.

CONTRAINDICATION

Absolute contraindication are hypercalcaemia resulting from myeloma, bone metastases or other malignant bone disease, sarcoidsis, primary hyperparathyroidism, vitamin D over-dosage and severe renal failure, Hypersensitivity to any of the tablet ingredients.
Use in caution in insulin-dependent diabetics with aspirin sensitive asthma.

WARNING AND PRECAUTIONS

Omega-3 fatty acids may have antithrombotic activity at high doses and in patients susceptible to bleeding. Therefore, they should be given with caution to patients with haemorrhagic disorders or to those receiving anticoagulants or other drugs affecting coagulation.

There is some evidence to suggest that fish oil supplements may adversely affect patients with aspirin sensitive asthma and that doses of Omega-3 fatty acids above 5g/day may cause mild deterioration of glycaemic control in noninsulin dependent diabetic patients causing a slight rise in glucose levels.

Caution is required in hepatic impairment, particularly if receiving high doses. It is advisable that patients with hepatic impairment do not receive high doses.

Patients with mild to moderate renal failure or mild hypercalciuria should be supervised carefully including periodic checks of plasma calcium levels and urinary calcium excertion. In the patients with a history of renal stones urinary calcium excretion should be measured to exclude hypercalciuria.

With long-term treatment it is advisable to monitor serum and urinary calcium levels and kidney function, and reduce or stop treatment temporarily if urinary calcium exceeds 7.5 mmol/ 24 hours (300mg/24 hours).

Renal Impairment
Although only small amounts of a vitamin D dose are recovered in the urine, metabolic conversion to cacitriol is reduced and higher doses are generally required in most conditions.

Hepatic Impairment
Pharmacokinetic data are lacking. However, intestinal absorption may be markedly impaired; conversion to 25 OHD may also be reduced significantly, with the requirement of high doses.

DRUG INTERATIONS

In view of a potential effect on bleeding time and platelet aggregation, great care should be exercised in patients on concomitant anticoagulation therapy or receiving other drugs which may affect coagulation factors, e.g. aspirin, warfarin, cephalosporin.

Thiazide diuretics: The risk of hypercalcaemia should consider in patients taking thiazide diuretics since these drugs can reduce urinary calcium excretion.

Hypercalcaemia must be avoided in digitalized patients. Certain foods (e.g. those containing oxalic acid, phosphate or phytinic acid) may reduce the absorption of calcium.

Phenytoin or barbiturates: Concomitant treatment with phenytoin or barbiturates can decrease the effect of vitamin D because of metabolic activation.

Glucocorticoids: Concomitant use of glucocorticoids can decrease the effect of vitamin D.

Digitalis and other cardiac glycosides: The effects of digitalis and other cardiac glycosides may accentuated with the oral administration of calcium combined with vitamin D. Strict medical supervision is needed and, if necessary monitoring of ECG and calcium is required.

Calcium salts may reduce the absorption of thyroxine, bisphosphonates, sodium fluoride, quinolone or tetracycline antibiotics or iron.

ADVERSE REACTIONS

As most undesirable effects are based on post-marketing spontaneous reporting, precise frequency estimation is not possible.

Gastrointestinal disorders: particularly at high doses, e.g. eructation, fishy after-taste, nausea, vomiting, diarrhoea, constipation.

Skin reactions: acne, eczema.

Moderate increases in hepatic transaminases have been reported in patients with hypertriglyceridemia.

G.I.T.: The most frequency reported side-effects resulting from postmarketing experience with Calcium with vitamin D_3 and mineral formuations were gastrointestinal and include abdominal pain, vomiting, flatulence, nausea, constipation.
Hepatic: None

Cardiovasculor: Tachycardia and palpitation.

Renal: The higher doses of calcium with vitamin D_3 have been associated with hypercalciuria.

Hypersensitivity Reaction (Allergic): Some patients may elicit allergic reactions those who are hypersensitive to any of the ingredient of formulation.

OVERDOSAGE

Acute or long-term overdose can cause hypervitaminosis D and hypercalcaemia. Hypercalcaemia gives the following symptoms: nausea, vomiting, thirst, polidipsia, poliuria, constipation. Chronic overdose can lead to vascular and organ calcification as a result of hypercalciamia.

Treatment
Treatment is symptomatic and supportive. All treatment with calcium and vitamin D should be rehydration should be performed.

DOSAGE AND ADMINISTRATION

Take one Capsule (Formula A) & one Tablet (Formula B) together once or twice in a day, or as directed by the Physician.

PREGNANCY AND LACTATION

There has been no reported experience of the use of Omega-3 fatty acids in pregnancies or breast feeding.

It should therefore only be given during pregnancy when benefits outweigh risks.

During pregnancy and lactation treatment with Megashelcal should be under the supervision of a physician.

Over doses of vitamin D have shown teratogentic effects in pregnant animals. However, there have been no studies on the use of this medicinal product in human pregnancy and lactation. Vitamin D and its metabolites pass into the breast milk.

Geriatric Use
In the treatment of ostomalacia, daily doses of 1000 international units of vitamin D_3 significantly increase calcium absorption in patients below the age of 70 years.

EXPIRY DATE
Two years from the date of manufacturing.

STORAGE
Store in a cool and dry place. Protect from light.

MARKETED BY:
TORRENT PHARMACEUTICALS LTD.
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