**FOSTEUM PLUS®** Capsules
calcium compounds (dicalcium malate and pentacalcium hydroxide triphosphate) (500 mg)
phosphate (70 mg)
genistein aglycone (27 mg)
citrated zinc bisglycinate (20 mg)
trans-menaquinone-7 (90 µg)
cholecalciferol (400 IU)

*Fosteum PLUS® is a specially formulated prescription medical food product for the clinical dietary management of the metabolic processes of osteopenia and osteoporosis.* ***Fosteum PLUS must be administered under physician supervision.***

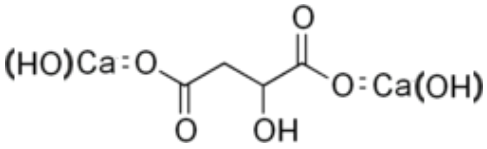
## DESCRIPTION

Fosteum PLUS consists of a specially formulated proprietary blend of dicalcium malate and pentacalcium hydroxide triphosphate, sodium phosphate, high purity genistein aglycone from a natural, non-soy source, citrated zinc bisglycinate, trans-menaquinone-7 (vitamin $K_2$), and cholecalciferol (vitamin $D_3$). Genistein aglycone reduces osteoclast activity and stimulates osteoblast activity. Citrated zinc bisglycinate works synergistically with genistein aglycone, while both citrated zinc bisglycinate and vitamin $D_3$ also work independently to promote mineralization activity in bone. Vitamin $K_2$ works with vitamin $D_3$ in aiding bone-building enzymes in the deposition of calcium in bone during remodeling. Vitamin $D_3$ also facilitates calcium absorption from the intestine.

## CALCIUM COMPOUNDS

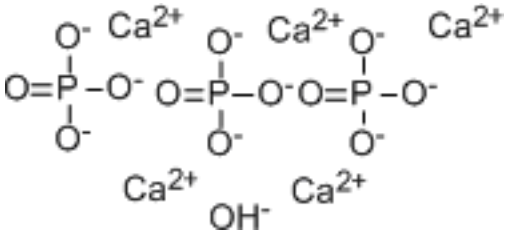
### DICALCIUM MALATE

Each Fosteum PLUS capsule contains 200 mg of dicalcium malate for a total daily intake of 400 mg. Dicalcium malate is chemically described as calcium 2,4-dihydroxy-4-oxobutanoate. The formula for dicalcium malate is $Ca_2C_4H_6O_7$; its molecular weight is 246.2. The structural formula is:



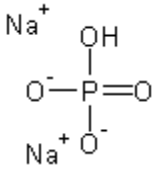

### PENTACALCIUM HYDROXIDE TRIPHOSPHATE

Each Fosteum PLUS capsule contains 300 mg of pentacalcium hydroxide triphosphate for a total daily intake of 600 mg. The formula for pentacalcium hydroxide triphosphate is $(Ca_5(OH)(PO_4)_3)$; its molecular weight is 502.31. The structural formula is:



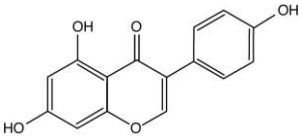
**PHOSPHATE**

Each Fosteum PLUS capsule contains 70 mg of phosphate for a total daily intake of 140 mg phosphate. Twenty-three (23) mg comes from sodium phosphate dibasic and 47 mg comes from pentacalcium hydroxide triphosphate (see above for structural formula). The empirical formula for sodium phosphate dibasic is $Na_2HPO_4$; its molecular weight is 141.96. The structural formula is:



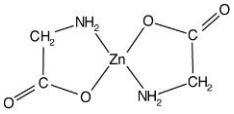
**GENISTEIN AGLYCONE**

Each Fosteum PLUS capsule contains 27 mg of genistein aglycone (genistein), isolated from a botanical non-soy source, for a total daily intake of 54 mg. In clinical trials, this level of intake was shown to increase bone mineral density (BMD). Genistein is chemically described as 4',5,7-trihydroxyisoflavone or 5,7-dihydroxy-3-(4-hydroxyphenyl)-4H-1-benzopyran-4-one. It is the aglycone form of the glucoside isoflavone molecule genistein. The formula of genistein is $C_{15}H_{10}O_5$: The molecular weight is 270.2. The structural formula is:



**CITRATED ZINC BISGLYCINATE**

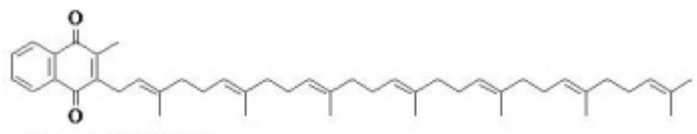
Each Fosteum PLUS capsule contains 20 mg citrated zinc bisglycinate, a glycine amino acid chelate of zinc, formed in the presence of citric acid that provides approximately 4 mg of elemental zinc per capsule. Zinc is an essential mineral co-factor required by enzymes involved in bone metabolism and has important physiological functions in other tissues throughout the body. Elemental zinc has also been shown to have synergistic effects with genistein on bone formation. This zinc bisglycinate, formed in the presence of citric acid, has been shown to have improved absorption over inorganic zinc salts, such as zinc sulfate. Zinc bisglycinate, a chelate of zinc, is complex with an empirical formula of $C_4H_8O_4Zn$; its molecular weight is 215.5. The structural formula is:



When generated in the presence of citric acid, citrate and glycinate ions (not shown) participate in this structure, forming citrated zinc bisglycinate, contributing to the complexity of the molecule.

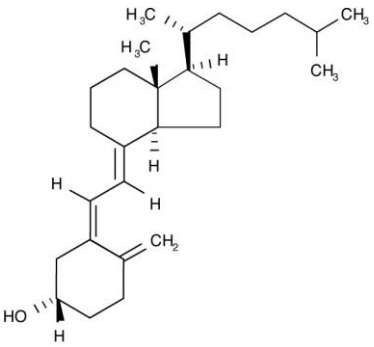
**TRANS-MENAQUINONE-7**

Each Fosteum PLUS capsule contains 90 µg of vitamin $K_2$ as pure trans-menaquinone-7 crystals for a total daily intake of 180 µg. Vitamin $K_2$ is chemically described as2-[(2E,6E,10E,14E,18E,22E) -3,7,11,15,19,23,27-hepta-methyloctacosa-2,6,10,14,18,22,26-heptaenyl]-3-methylnaphthalene-1,4-dione (IUPAC convention) The formula for menaquinone-7 is $C_{46}H_{64}O_2$; its molecular weight is 649.0. The structural formula is:



**CHOLECALCIFEROL**

Each Fosteum PLUS capsule contains cholecalciferol equivalent to 400 IU vitamin $D_3$. Vitamin $D_3$ is the natural form of the vitamin produced when skin is exposed to the sun. Vitamin $D_3$ is necessary for proper absorption of calcium from the intestine and the use of absorbed calcium in the mineralization of bone. Cholecalciferol is the natural precursor of calcitriol (1,25-dihydroxy-cholecalciferol), the physiologically active form of vitamin D. It is described as (3ßµ,5Z,7E)-9,10-secocholesta-5,7, 10(19)-triene-3-ol. The empirical formula is $C_{27}H_{44}O$; its molecular weight is 384.6. The structural formula is:




**OTHER INGREDIENTS**

Fosteum PLUS contains the following other ingredients as excipients: micro-crystalline cellulose, magnesium stearate, and silicon dioxide. The capsule is bovine gelatin, with titanium dioxide and sodium copper chlorophyllin for the capsule color. Fosteum PLUS does not contain fructose, glucose, sucrose, lactose, gluten, maltodextrin, tree nuts, peanuts, soy, flavors or products of seafood origin.

## MEDICAL FOOD

Medical Food products are used under a physician's supervision for the dietary management of diseases in patients with particular medical or metabolic needs due to their disease or condition. The U.S. Congress defined "medical food" in the Orphan Drug Act and Amendments of 1988 as "a food which is formulated to be consumed or administered enterally under the supervision of a physician, and which is intended for the specific dietary management of a disease or condition for which distinctive nutritional requirements, based on recognized scientific principles, are established by medical evaluation." Fosteum PLUS has been developed, manufactured and labeled in accordance with both the statutory and the FDA regulatory definition of a medical food. Fosteum PLUS is to be used only under a physician's supervision.

## GENERALLY RECOGNIZED AS SAFE

The ingredients in Fosteum PLUS are Generally Recognized As Safe (GRAS). This is the statutory safety standard that the U.S. Food and Drug Administration (FDA) require of all ingredients added to food products. The standard for an ingredient to achieve GRAS status requires technical demonstration of non-toxicity and safety, general recognition of safety through widespread usage and agreement of that safety by experts in the field.

## LOW BONE MASS AND OSTEOPOROSIS

Low bone mass (osteopenia) and osteoporosis are gradations of bone loss. Low bone mass may progress to osteoporosis. Low bone mass and osteoporosis occur when the metabolic processes of normal bone turnover are unbalanced in favor of resorption activity. The World Health Organization (WHO) defines low bone mass as a T-score (by dual energy absorption technology, DXA) between -1.0 and -2.5. Osteoporosis is defined at a T-score lower than -2.5.

## CLINICAL PHARMACOLOGY

### Mechanism of Action

Fosteum PLUS acts by restoring and maintaining the balance of bone turnover toward normal levels in patients with osteopenia and osteoporosis. Calcium and phosphate are necessary for proper bone formation. Preclinical and clinical data suggest that the genistein in Fosteum PLUS reduces

osteoclast-mediated bone resorption and stimulates the bone forming activity of osteoblasts. The zinc in Fosteum PLUS acts synergistically with the genistein to retard maturation of osteoclasts and promote the maturation and number of osteoblasts. Menaquinone-7 has been shown to activate osteocalcin by enhancing the replacement of carboxyl groups for glutamic acid residues on osteocalcin thereby increasing its binding to calcium for proper bone mineralization. Cholecalciferol improves the absorption of calcium and its deposition into the mineral matrix of bone.

Osteopenia and osteoporosis most commonly occur because of hormonal changes associated with the aging process or the use of certain classes of drugs. Bone loss associated with these conditions is primarily due to the metabolic imbalance that occurs when osteoclast activity is greater than osteoblast activity. The imbalance of bone resorption in excess of bone formation is progressive and often leads to fractures. These minimal trauma fractures may lead to significant morbidity and mortality. Clinical dietary management of the metabolic processes underlying osteopenia and osteoporosis helps to restore the balance between bone resorption and bone formation and consequently increases bone mineral density over time.

**Calcium and Phosphate**
The calcium in Fosteum PLUS is essential for building bone. Calcium is part of the structure of bone in the form of hydroxyapatite (pentacalcium hydroxide triphosphate). Proper bone remodeling requires both calcium and phosphate consumed in the diet. Low phosphate intake even in the presence of adequate calcium consumption has been shown to decrease osteoblast function and increase osteoclast activity resulting in net bone loss or decrease in bone mineral density. New bone mineralization consumes calcium and phosphate at a molar ratio of approximately 1.6:1. Fosteum PLUS contains a molar ratio of calcium to phosphate that approximates this number.

**Genistein Aglycone**
The genistein in Fosteum PLUS decreases the maturation of osteoclasts and promotes the formation of osteoblasts from progenitor stem cells to increase their number and activity in bone. The net effect is an enhancement of bone formation that restores bone remodeling toward normal levels and results in an increase in BMD over time. More specifically, preclinical studies suggest the following mechanisms of action: Genistein acts to reverse the effects of estrogen loss by decreasing cytokine production and increasing transforming growth factor ß (TGFß) levels. This results in a decrease in receptor activator of nuclear factor kappa B ligand (RANK-L) production, an increase in osteoprotegerin (OPG) levels, and interruption of the interaction between RANK and RANK-L that produces an overall decrease in osteoclast activity. Genistein also increases insulin-like growth factor-1 (IGF-1) leading to an increased number of proto-osteoblasts developed from mesenchymal stem cells. Genistein restores endothelial cell signals resulting in increased recruitment of these precursor cells to form osteoblasts. Genistein also reverses early apoptosis of osteoblasts. These actions likely produce a net increase in osteoblast activity and concomitant decrease in osteoclast activity. In clinical trials, the genistein in Fosteum PLUS decreased urinary levels of the bone resorption markers: urinary and serum collagen type 1 cross-linked C-telopeptide (CTX), deoxypyridinoline (DPYR) and pyridinoline (PYR), and increased serum levels of the bone formation markers: bone-specific alkaline phosphatase (BAP), osteocalcin (OC), and IGF-1.

**ZINC (ELEMENTAL)**
Zinc has a positive effect on bone formation. The zinc in Fosteum PLUS is the citrated bisglycinate form, which has been shown to have improved absorption from the intestine compared to inorganic zinc salts. Cell cultures of rat femoral-metaphyseal tissue treated with zinc and genistein produced a greater increase in BAP, deoxyribonucleic acid (DNA), and bone calcium content compared with either agent alone. Other studies have demonstrated that genistein and zinc produce synergistic effects on osteoclast apoptosis and bone mineralization. Animal studies support these findings by showing that the combination of zinc and genistein increases mineralization in bone over genistein alone. In both men and women, zinc was shown to potentiate the effect of high genistein-containing fermented food on bone markers by further increasing the levels of BAP and OC. Based on these data, genistein and zinc increase osteoblast activity while decreasing osteoclast activity to a greater extent than either genistein or zinc alone.

**Trans-Menaquinone-7**
Trans-menaquinone-7 aids in the mineralization of bone by acting as a cofactor for gamma-carboxylase, an enzyme that substitutes carboxyl groups for glutamic acid (glutamyl) residues on a series of proteins collectively called Gla proteins. This carboxylation renders them physiologically active. Three Gla proteins have been identified in bone. Gla-osteocalcin (Gla-OC) residues bind calcium ($Ca^{2+}$) to be incorporated into hydroxyapatite crystals. Matrix Gla-protein forms a significant part of the structural matrix in bone into which the apatite is incorporated. Protein-S, a protein produced by osteoblasts and involved in bone remodeling homeostasis, is also vitamin K-dependent. In the absence of adequate vitamin K (or in the presence of warfarin), much of the OC remains uncarboxylated (un-OC) and $Ca^{2+}$ binding and deposition in bone is inadequate. Increased serum un-OC has been associated in humans with decreased BMD. Vitamin $D_3$ and menaquinone-7 act synergistically on the molecular level to increase the production of OC, modulate the production of OPG, RANK and RANKL, and inhibit immature osteoclast differentiation.

**Cholecalciferol**
Cholecalciferol is converted in the body to calcitriol, the physiologically active form of vitamin D. Calcitriol regulates calcium and phosphate absorption and modulates serum calcium, renal calcium and phosphate excretion, bone formation and bone resorption. Vitamin D deficiency is associated with a negative calcium balance, increased parathyroid hormone levels, bone loss and increased risk of skeletal fracture. Severe deficiency results in hyperparathyroidism, hypophosphatemia, proximal muscle weakness, bone loss, and osteomalacia.

## METABOLISM

### CALCIUM COMPOUNDS
Calcium is absorbed most efficiently in separate doses of 500 mg or less. Upon dissociation in the stomach, calcium and phosphate are absorbed in the duodenum and proximal small intestine. Blood calcium levels are tightly regulated by parathyroid hormone (PTH) and calcitonin. PTH increases calcium blood concentration while decreasing phosphate concentrations. Calcitonin decreases serum calcium and phosphate levels in the blood. Therefore, the addition of phosphate with calcium is essential since both PTH and calcitonin can lead to decreases in phosphate, an essential component of bone. The combination of calcium and phosphate in Fosteum PLUS provides the proper balance for net bone building.

### GENISTEIN AGLYCONE
The genistein in Fosteum PLUS is freely absorbed in the gut where it is at least partly converted to one metabolite, 7-O-beta-glucuronide, before it crosses the mucosa from the intestinal lumen. In hepatic first pass metabolism, genistein is converted *via* a two-stage process involving initial CYP450-mediated hydroxylation, followed by glucuronidation and sulfonation to the principal conjugated circulating metabolites. Genistein metabolites are converted back into the aglycone form in a variety of tissues. The aglycone is believed to be the principal active form, but conjugates have shown some activity in estrogen-receptor binding assays. Genistein and its conjugates are excreted *via* urine and bile.

### TRANS-MENAQUINONE-7
Vitamin K occurs in two isomeric forms and several sub-isomers. Vitamin $K_2$ (also known as menaquinone) has primary action on bone and vasculature. Vitamin $K_1$ (also known as phylloquinone) exerts its primary action on the clotting sequence (thrombin, prothrombin). Vitamin $K_2$ is present in meat, milk products, cheese, and eggs, while Vitamin $K_1$ is found primarily in green leafy vegetables and vegetable oils. In the liver, menaquinone enters hepatocytes by endocytosis, binding to low density lipoprotein receptor (LDLR) and lipoprotein related receptors (LRP). Menaquinone is further combined with very low-density lipoprotein and excreted into the circulation. Circulating menaquinone-lipoprotein complexes bind to LDLR and LRP on the surface of osteoblasts in bone matrix to deliver menaquinone to bone building cells.

### CITRATED ZINC BISGLYCINATE
Citrated zinc bisglycinate consists of zinc chelated by glycine in the presence of citric acid. Once absorbed, the zinc is released from the chelate. Subsequently, glycine is utilized in normal protein metabolism and zinc is bound to albumin as well as blood cells and distributed throughout the body. The citrate is absorbed and utilized in the tricarboxylic acid cycle (Krebs cycle). The majority of zinc in the human body is found in muscle and bone. Excretion occurs predominantly *via* the feces.

**CHOLECALCIFEROL**

Ultraviolet light acts on 7-dehydrocholesterol (provitamin $D_3$) in skin, where it is converted to 9,10-secosterol (previtamin $D_3$). Previtamin $D_3$ is converted into 25-hydroxycholecalciferol in the liver by the P450 enzyme CYP27. This molecule is further converted in the kidney by the P450 enzyme CYP27B1 to the active hormone, 1,25-dihydroxycholecalciferol (calcitriol). Vitamin $D_3$ stimulates the absorption of both calcium and phosphate in the upper intestine.

## CLINICAL EXPERIENCE

**HEPATIC AND RENAL EFFECTS**

In clinical studies, the effects of genistein on blood chemistries, including hepatic and renal function measures, were compared in post-menopausal subjects receiving genistein plus calcium carbonate (calcium) and vitamin $D_3$ with post-menopausal, age-matched subjects receiving only calcium and vitamin $D_3$. No change in laboratory values were noted over a three year period in either group and all measures remained within normal limits.

There are no known adverse hepatic or renal effects of menaquinone-7, citrated zinc bisglycinate or cholecalciferol.

**EFFECTS ON REPRODUCTIVE TISSUES**

Effects of the genistein in Fosteum PLUS on breast density, vaginal cytology and endometrial thickness were tested in long-term (3 years) double-blind, placebo-controlled clinical trials. One trial with 30 post-menopausal subjects in each arm found that genistein did not affect endometrial thickness over a one year period compared to placebo. In other controlled trials, daily administration of 54 mg of genistein over one, two and three year periods produced no increases in endometrial thickness or breast density in post-menopausal women. Furthermore, a subset of 119 post-menopausal women showed no change in vaginal cytology following two years of daily genistein therapy. Genistein was shown to be equivalent in women with endometrial hyperplasia to norethisterone acetate for decreasing signs of bleeding, endometrial thickness and improving uterine cytology. These data suggest that the genistein in Fosteum PLUS does not produce adverse estrogenic effects in reproductive tissues.

**CARDIOVASCULAR SAFETY**

Dietary intake of calcium should be considered when dosing Fosteum PLUS, which contains 500 mg of dicalcium malate and pentacalcium hydroxide triphosphate per capsule (175 mg of elemental calcium). Post-menopausal women with bone loss should consume no more than 1,200 to 1,400 mg of elemental calcium per day. Excess calcium has recently been shown in observational studies to increase the risk of cardiovascular dysfunction, including myocardial infarction and stroke.

In a study of 60 post-menopausal subjects, the cardiovascular markers of those receiving the genistein in Fosteum PLUS were compared to a matched group receiving placebo. Homocysteine and C-reactive protein (CRP) were assessed at baseline and again at 6 months. No statistically significant differences were seen between groups. Soluble intercellular adhesion molecule-1 (ICAM), vascular cell adhesion molecule-1 (VCAM), fibrinogen and F2-isoprostane levels were assessed at baseline and again at 12 and 24 months in 389 post-menopausal subjects randomized to receive either genistein, calcium and vitamin $D_3$ (product), or calcium and vitamin $D_3$ only (placebo). At both 12 and 24 months, the levels of all four cardiovascular markers were reduced in the genistein group compared to both baseline and placebo at each time point. No significant changes in lipid profile were observed in either the genistein or the placebo group over the course of the study. These data indicate that genistein does not adversely affect markers of cardiovascular risk. An additional study of 53 post-menopausal women measured changes in flow-mediated vasodilation and plasma nitric oxide status. The genistein in Fosteum PLUS significantly increased plasma nitrite/nitrate levels and reduced levels of endothelin-1 compared to placebo. After 12 months of use, forearm blood flow increased significantly during reactive hyperemia in the genistein group compared to placebo. Flow-mediated dilation in the proximal and distal brachial arteries both increased significantly after genistein administration. The purified genistein in Fosteum PLUS improved endothelial function in a cohort of post-menopausal women. Finally, in post-menopausal women with metabolic syndrome (n=120),

genistein in Fosteum PLUS was shown to statistically decrease LDL and triglycerides, while increasing HDL against placebo.

In large observational studies, menaquinone-7 was shown to reduce arterial calcium accumulation and protect against cardiovascular dysfunction. In the cardiovascular system, deficiency of carboxylated matrix Gla protein (MGP) is associated with arterial calcification and the progression of vascular disease. Menaquinone-7 increases the circulating concentrations of carboxylated MGP.

#### MENOPAUSAL SYMPTOMS

In three published studies with a combined enrollment of more than 300 post-menopausal women, the genistein in Fosteum PLUS progressively reduced the number of symptomatic vasomotor episodes by an average of more than 50% at the 24 month follow-up. In these studies, vasomotor symptoms were unchanged in the placebo groups.

#### BLOOD GLUCOSE AND INSULIN RESISTANCE

The genistein in Fosteum PLUS was also found to significantly reduce fasting glucose and insulin levels, as well as insulin resistance, in 198 post-menopausal women over a 2 year period and in a subset of 71 patients over a 3 year period when compared to placebo. In a separate study of post-menopausal women with metabolic syndrome (n=120), the genistein in Fosteum PLUS was statistically shown to decrease fasting blood glucose and insulin as well as insulin resistance versus placebo.

## DRUG INTERACTIONS

#### CALCIUM COMPOUNDS

Thiazide diuretics inhibit renal calcium excretion. Care should be taken to monitor serum calcium in patients with high dietary calcium intake, and those who are taking both supplemental calcium and thiazides.

#### GENISTEIN AGLYCONE

The genistein in Fosteum PLUS was tested in *in vitro* pooled human liver microsome assays for CYP1A2, 2A6, 2C8, 2C9, 2D6, and 3A4. Inhibition of the 1A2, 2A6, 2D6 and 3A4 isozymes was low, however, inhibition of CYP450 2C8 and 2C9 was observed with IC50s of 2.5 and 2.8 µM, respectively. Results from a steady-state pharmacokinetic study in post-menopausal women showed that the level of circulating genistein was in the low nanomolar range and undetectable at most time points in many subjects. These data suggest that circulating genistein does not reach the concentration required to produce any clinically significant interactions with co-administered drugs. The effects of the principal circulating metabolites of genistein on CYP450-mediated metabolism are currently unknown. .

#### TRANS-MENAQUINONE-7

Warfarin specifically antagonizes the carboxylation of Gla proteins thus rendering them inactive. Warfarin therapy is associated with prolongation of the clotting sequence (usually measured by a prothrombin time and International Normalized Ratio or INR). Warfarin therapy is also associated with the development of osteopenia/osteoporosis and arterial calcification. The specific and rapidly acting antidote for bleeding associated with warfarin overdose is Vitamin $K_1$ (phylloquinone) by parental administration. In a study of young, healthy anti-coagulated patients on warfarin, addition of vitamin $K_2$ (menaquinone-7) resulted in a decrease in INR. There are no other known drug interactions for menaquinone-7. See precautions for recommendations regarding use in patients taking warfarin.

#### CHOLECALCIFEROL

Cimetidine, thiazides and anticonvulsants may increase catabolism of vitamin $D_3$. Cholestyramine and other bile acid sequestrants, as well as mineral oil, orlistat and olestra may impede absorption of vitamin $D_3$ from the intestine.

## TOXICITY

#### CALCIUM AND PHOSPHATE COMPOUNDS

Dietary intake of calcium should be considered when dosing Fosteum PLUS, which contains 350 mg of total elemental calcium when taken twice daily. Post-menopausal women with bone loss should consume no

more than 1,200 to 1,400 mg of elemental calcium per day from all sources. Recent studies have shown that excess calcium can increase the risk of myocardial infarction and stroke.

Dicalcium malate and pentacalcium hydroxide triphosphate in Fosteum PLUS have no known adverse hepatic effects. Patients with renal insufficiency have been shown to retain phosphate, which can lead to hyperphosphatemia which, in turn, may result in hypocalcemia due to precipitation of phosphate with the calcium in multiple tissues. Ectopic calcification, secondary hyperparathyroidism and renal osteodystrophy can occur in patients with renal insufficiency who consume both calcium and phosphate.

#### GENISTEIN AGLYCONE

Genistein showed no toxicity in rats following acute dosing up to 2000 mg/kg. Long-term toxicity studies up to 52 weeks duration using oral administration of 0-500 mg/kg/day in rats and dogs showed minimal adverse effects. From these studies, the no observed adverse effect level (NOAEL) for genistein in rats was determined to be 50 mg/kg/day and in dogs >500 mg/kg/day. These intake levels are at least 50-fold greater than the recommended human dose of the genistein in Fosteum PLUS on a mg/kg basis.

#### ZINC (ELEMENTAL)

The National Academy of Sciences (NAS) upper acceptable limit for self-administration is 40 mg/day of elemental zinc, the equivalent of ten Fosteum PLUS capsules per day. Zinc is considered acutely toxic at 200 mg elemental zinc per day, the equivalent of 50 Fosteum PLUS capsules.

#### CHOLECALCIFEROL

Cholecalciferol may produce toxicity with long term, high-dose consumption. While medical doses of vitamin $D_3$ up to 10,000 IU per day are sometimes administered under physician supervision, the upper acceptable limit for self-administration is 2,000 IU per day according to the Daily Reference Intakes (DRI) of the Institute of Medicine published by the NAS in 2004. Signs and symptoms of vitamin D toxicity include hypercalcemia, hypercalciuria, anorexia, nausea, vomiting, polyuria, polydipsia, weakness and lethargy. Serum and urine calcium levels should be monitored in patients with suspected vitamin D toxicity, and therapy initiated promptly in symptomatic patients

## SPECIAL POPULATIONS

#### PREGNANT OR NURSING WOMEN

Fosteum PLUS has not been tested in pregnant or nursing women.

#### MALES

Fosteum PLUS has not been studied for its effect on bone in human males. No specific studies on genistein aglycone and feminization in human males exist.

#### PEDIATRICS

Fosteum PLUS has not been tested in pediatric patients.

## INDICATIONS AND USAGE

#### INDICATIONS

Fosteum PLUS is indicated for the clinical dietary management of the metabolic processes of osteopenia and osteoporosis.

#### USAGE

Fosteum PLUS may be taken with additional calcium and/or vitamin $D_3$ if directed by a physician after determining dietary intake of both nutrients. In clinical trials of the genistein (54 mg/day) used in Fosteum PLUS, patients received 1,000 mg of calcium carbonate and 800 IU vitamin $D_3$ per day in two divided doses. See Dosage and Administration for additional information.

#### INTERACTIONS WITH FOOD

Fosteum PLUS can be taken with or without other foods. Fosteum PLUS may be taken with any beverage desired.

## PRECAUTIONS AND CONTRAINDICATIONS

### GENERAL

Causes of osteopenia or osteoporosis other than menopause or aging should be considered.

### HYPERSENSITIVITY

Fosteum PLUS is contraindicated for anyone having a hypersensitivity to any ingredient in the product.

### PATIENTS WITH CANCER

Fosteum PLUS has not been specifically studied in patients with a history of cancer of the breast or reproductive organs. Major studies on isoflavone intake have been published including one epidemiological study involving 18,312 postmenopausal women who were followed for an average of 9.2 years. Based on these findings, Fosteum PLUS may be suitable for the management of osteopenia and osteoporosis in these populations. The decision to use Fosteum PLUS in these clinical situations should be made in consultation with the patient's physician.

### VITAMIN D DEFICIENCY / OVERPRODUCTION

Fosteum PLUS is not intended to treat vitamin $D_3$ deficiency, generally characterized in the literature by serum levels of 25-hydroxycholecalciferol below 9 ng/mL.

In patients suffering from diseases associated with unregulated overproduction of calcitriol, supplemental vitamin $D_3$ may worsen hypercalcemia and/or hypercalciuria. Therefore, Fosteum PLUS is not recommended in these patients.

### PREGNANCY

Animal studies suggest that genistein may produce developmental abnormalities of the male and female genital tracts if consumed during early stages of pregnancy. Effects in infants of nursing mothers are uncertain. Therefore, Fosteum PLUS is not recommended in pregnant and lactating women. Women capable of becoming pregnant should use appropriate contraception when taking Fosteum PLUS. The genistein in Fosteum PLUS has not been tested in women capable of becoming pregnant.

### WARFARINIZED PATIENTS

Vitamin $K_1$(phylloquinone) is a specific antagonist of warfarin on the Gla proteins of the clotting system. Vitamin $K_2$ (menaquinone) has similar, but weaker, effects on these proteins. The few published studies available suggest that doses of 300 µg/day may be required for clinically significant warfarin antagonism to occur, but these data vary greatly depending on individual dietary intake of vitamin K containing foods. Primus recommends that patients taking warfarin should NOT use Fosteum PLUS. However, if a physician feels that the use of Fosteum PLUS is indicated, the INR should be followed very carefully, probably at least twice weekly, and warfarin dose adjustments made as required until the INR is stabilized. The patient should also be given dietary advice to avoid high vitamin K containing foods and be advised not to alter or miss a dose of Fosteum PLUS. If a dose alteration is unavoidable, the patient should promptly see the physician for repeat monitoring.

## ADVERSE EVENTS

### CALCIUM COMPOUNDS

Neither dicalcium malate nor pentacalcium hydroxide triphosphate are known to cause specific adverse events. All calcium can be constipating, especially if used in excess. Proper hydration is recommended with any calcium-containing product.

### GENISTEIN AGLYCONE

In a three-year clinical trial, 389 subjects were randomized to either genistein plus calcium and vitamin $D_3$ n=198, or calcium and vitamin $D_3$ alone n=191. A total of 52 subjects in both groups discontinued due to adverse events. Study discontinuation in these subjects was due to gastrointestinal symptoms, including abdominal and epigastric pain, dyspepsia, vomiting and constipation. Discontinuation was reported in both

groups. The incidence of adverse events was statistically higher in the genistein group throughout the study. The major adverse events are shown in the table below without attribution of causality.

| Adverse Events | Year 1 | | Year 2 | | Year 3 | |
|---|---|---|---|---|---|---|
| | Genistein +Ca/$D_3$ (n=178) | Ca/$D_3$ (n=172) | Genistein +Ca/$D_3$ (n=150) | Ca/$D_3$ (n=154) | Genistein +Ca/$D_3$ (n=71) | Ca/$D_3$ (n=67) |
| Abdominal Pain | 4 (2.2%) | 2 (1.1%) | 2 (1.3%) | 1 (0.6%) | 1(1.4%) | 1(1.5%) |
| Dyspepsia | 2 (1.1%) | 1 (0.6%) | 7 (4.7%) | 2 (1.3%) | 2(2.8%) | 1(1.5%) |
| Constipation | 5 (2.8%) | 3 (1.7%) | 8 (5.3%) | 3 (1.9%) | 2(2.8%) | 1(1.5%) |

Some of these adverse event occurrences may be attributable to the intake of 1,000 mg per day of calcium carbonate by subjects in both groups. Taking Fosteum PLUS with food may reduce or eliminate some gastrointestinal symptoms.

#### TRANS-MENAQUINONE-7

In clinical studies of menaquinone-7, adverse events have been similar to placebo. Small increases in coagulation test values compared to placebo were noted, although these values remained within normal ranges.

## PHARMACOKINETICS

#### GENISTEIN AGLYCONE

To determine the disposition of the genistein in Fosteum PLUS, a steady-state pharmacokinetic (PK) study was conducted in post-menopausal women aged 50-66. Ten subjects took genistein without food (fasted group) and 10 subjects took genistein with food (fed group) twice daily (54 mg total) for seven (7) days. On the eighth day, blood was collected at 1, 2, 3, 4, 6, 8, 10, 12, 24, 36, 48 and 96 hours after ingesting genistein with (fed group) or without (fasted group) food. Concentrations of serum aglycone (protein bound and unbound) and total genistein (aglycone plus circulating conjugated forms) were determined at each time point for standard pharmacokinetic analyses.

Levels of free genistein aglycone were in the low nanomolar range and below the level of quantification in several subjects. Therefore, meaningful pharmacokinetic parameters could not be calculated from the data. Consistent with previous studies, the majority of circulating genistein existed in the conjugated form. Pharmacokinetic analyses for total genistein reported in the table below revealed no significant difference in any parameter between the fed and fasted groups, suggesting that Fosteum PLUS may be taken with or without food. The serum half-life (t1/2) among all subjects was 9.6 hours. Based on this profile, BID dosing is recommended.

| Prandial State | N | Total Genistein | Mean ±SD |
|---|---|---|---|
| Fasting | 10 | Cmax (ng/mL)<br>Tmax (hours)<br>T1/2 (hours)<br>AUC | 837.5 ± 414.8<br>2.0 ± 1.2<br>8.1 ± 4.9<br>9622.8 ± 5843.0 |
| Fed | 9 | Cmax (ng/mL)<br>Tmax (hours)<br>T1/2 (hours)<br>AUC | 671.1 ± 297.1<br>3.3 ± 1.5<br>11.2 ± 3.6<br>11045.2 ± 6208.6 |

#### TRANS-MENAQUINONE-7

A single-dose pharmacokinetic study demonstrated that menaquinone-7 is well absorbed with a maximal serum concentration (Tmax) at 6 hrs. A separate single-dose pharmacokinetic study showed a Tmax at 4 hrs. Both studies showed a biphasic depletion of menaquinone-7 with half of the molecule excreted in approximately 10 hours, but not reaching baseline for 3 days. Half-life (T1/2) estimations are difficult to calculate due to the biphasic kinetics.

## CLINICAL STUDIES

### DIETARY MANAGEMENT OF OSTEOPENIA AND OSTEOPOROSIS

*Effect on Bone Mineral Density*

Efficacy of the genistein in Fosteum PLUS was demonstrated in a multi-center, double-blind, placebo-controlled clinical study of 389 randomized post-menopausal patients with osteopenia or osteoporosis (genistein n=198; placebo n=191). All subjects received calcium (1,000 mg/day) and vitamin $D_3$ (800 IU/day) in two divided doses.

*Mean Percent Change in BMD over 24 Months*

| SITE | 12 months vs. baseline | | 24 months vs. baseline | |
|---|---|---|---|---|
| | **Genistein +Ca/$D_3$ (n=178)** | **Ca/$D_3$ (n=172)** | **Genistein +Ca/$D_3$ (n=150)** | **Ca/$D_3$ (n=154)** |
| Femoral Neck | 2.4% | -2.2% | 5.1% | -5.3% |
| Lumbar Spine | 2.9% | -3.6% | 5.8% | -6.3% |

After two years, both lumbar spine and femoral neck showed significant increases in BMD relative to both baseline and placebo in patients who received genistein. In a third year extension, 138 patients continued on blinded study product. Patients taking the genistein in Fosteum PLUS showed a continued increase in BMD at both lumbar spine and femoral neck. In this cohort, 85% of the patients in the genistein arm showed increased BMD.

*Mean Percent Change in BMD over 24 and 36 Months (Extended Study Group)*

| SITE | 24 months vs. baseline | | 36 months vs. baseline | |
|---|---|---|---|---|
| | **Genistein +Ca/$D_3$ (n=71)** | **Ca/$D_3$ (n=67)** | **Genistein +Ca/$D_3$ (n=71)** | **Ca/$D_3$ (n=67)** |
| Femoral Neck | 5.2% | -5.4% | 7.0% | -7.5% |
| Lumbar Spine | 7.3% | -6.3% | 10.3% | -10.6% |

Measurement of bone markers supported the proposed mechanism of action. Levels of formation markers were increased, and levels of resorption markers were reduced in the genistein group compared with baseline as shown in the table below.

*Mean Percent Change in Bone Markers at 12, 24 and 36 Months vs. Baseline*

| | 12 months vs. baseline | | 24 months vs. baseline | | 36 months vs. baseline | |
|---|---|---|---|---|---|---|
| | **Genistein + Ca/$D_3$ (N=178)** | **Ca/$D_3$ (N=172)** | **Genistein + Ca/$D_3$ (N=150)** | **Ca/$D_3$ (N=154)** | **Genistein + Ca/$D_3$ (N=71)** | **Ca/$D_3$ (N=67)** |
| BAP | +32.7% | -0.8% | +38.5% | -1.1% | +45.3% | -1.2% |
| IGF-1 | +18.0% | -2.3% | +13.0% | +1.6% | +16.7% | -3.0% |
| PYR | -14.5% | -3.3% | -13.5% | -1.0% | -15.8% | -2.8% |
| DPYR | -12.4% | -1.2% | -10.2% | -0.9% | -14.1% | -3.0% |
| CTX | -24.9% | +2.3% | -35.5% | +2.9% | -43.7% | +6.2% |

Genistein's efficacy was also shown in a one year trial of 90 osteopenic or osteoporotic, post-menopausal subjects vs. placebo and vs. hormone replacement therapy (HRT). Baseline values were matched for all parameters. The BMD values at 12 months are shown in the table below:

*Mean Percent Change in BMD at 12 Months vs. Baseline*

| SITE | GENISTEIN (n=30) | HRT (n=30) | PLACEBO (n=30) |
|---|---|---|---|
| Femoral Neck | 3.6% | 2.4% | -0.7% |
| Ward's Triangle | 4.0% | 3.0% | -0.4% |
| Lumbar Spine | 3.0% | 3.8% | -1.6% |

#### TRANS-MENAQUINONE-7

In large epidemiological studies, low serum $K_2$ levels have been associated with increased risk of low bone mass and osteoporotic fractures. In a study, 94 osteoporotic postmenopausal women treated with HRT for >1year, were started on menaquinone. In 84 of the patients, BMD increased by 2.9% after 1 year, and reached and maintained a plateau of 5.4% increase (+/-1.2%) after 3 years. In the remaining 10 patients, BMD fell slightly after reaching a plateau. Multiple other studies have shown improvement of markers of bone metabolism with vitamin $K_2$ administration, and these findings were reflected in improvements in BMD and fracture rates. Other studies have suggested that vitamin $K_2$ improves bone quality independent of its effects on BMD.

Numerous epidemiological and interventional studies have demonstrated that vitamin MK-7 increases bone and plasma levels of the active (carboxylated) form of osteocalcin, increases bone mineral content (BMC) and, to a lesser extent, bone mineral density (BMD) and bone strength. Uncarboxylated osteocalcin (un-OC) levels have been shown to positively correlate with fracture risk. In one study of 195 women aged 70-101 years, 23% were found to have elevated levels of un-OC. 15 of which suffered a hip fracture in an 18 month follow-up period giving a relative risk of 5.9. Review articles and other reports, including a prospective longitudinal study of 7598 elderly women have demonstrated reduction in fracture risk independent of BMD suggesting MK-7improves structural bone quality. A 3 year randomized trial of 120 postmenopausal women treated with 180 mcg MK-7 daily vs.124 placebo treated women (published in 2013) found reduction of plasma un-OC of 58% in those given MK-7 vs. 4% in the placebo group. After 3 years the MK-7 treated group had significantly less bone loss in the femoral neck (p=0.023 for BMC and p=0.014 for BMD) and lumbar spine (p=0.001 for BMC and 0.111 for BMD). In the MK-7 group there was less loss of vertebral height in T10-12 (p=0.003) although no differences were seen in T7-9 and L1-3. One (1) clinical fracture occurred in the MK-7 treated women and 6 in the placebo group.

#### TRANS-MENAQUINONE-7 AND CORTICOSTERIOD-INDUCED BONE LOSS

In a short-term study (10 wks) of 20 patients, menaquinone halted prednisolone-induced loss of BMD in patients taking both trans-menaquinone-7 and prednisolone.

#### FRACTURE DATA

The studies performed on the genistein in Fosteum PLUS to date were not intended to assess new incident fractures. These studies showed reduced markers of bone resorption, increased markers of bone formation and increased BMD in clinical trials. Anecdotally, in the 389 patient clinical trial comparing genistein to placebo over a three-year period, there were three fractures of the sacrum in the placebo (calcium and vitamin $D_3$) group while no fractures were observed in the genistein group. Studies in animals have demonstrated an increase in bone quality including an increase in bone breaking strength and improvement in architecture on histological examination after genistein administration.
In epidemiological studies of populations with high serum concentrations of genistein and menaquinone, there is a large reduction in the observance of fracture when compared with populations demonstrating low concentrations of genistein and menaquinone. No specific clinical trials using fracture as an endpoint have been performed on either the genistein or the menaquinone-7 in Fosteum PLUS as the reported data on fracture came from food-based studies.

### OVER USAGE

#### CALCIUM COMPOUNDS

Supplemental calcium should be administered with caution in patients with high bone turnover states, such as Paget's disease, and in patients with a history of calcium containing urolithiasis, hyperparathyroidism and certain renal tubular abnormalities.

#### GENISTEIN AGLYCONE

There are no known cases of over usage of the genistein in Fosteum PLUS. Animal studies have shown that consuming the equivalent of 75 Fosteum PLUS capsules at one time did not produce adverse events. If an over usage were to occur, patients should be managed by systematic and supportive care as soon as possible following product consumption.

**TRANS-MENAQUINONE-7**
There are no known cases of over usage of the trans-menaquinone-7 in Fosteum PLUS. The 'no observed adverse effect level' (NOAEL) of menaquinone-7 administered orally in rats for 90 days was 10 mg/kg body weight/day. For a 60 kg human (132 lbs.), this is more than 300 times the dose present in a Fosteum PLUS capsule. If an over usage were to occur, patients should be managed by systematic and supportive care as soon as possible following product consumption.

**ZINC (ELEMENTAL)**
Zinc is considered acutely toxic at 200 mg elemental zinc per day, the equivalent of 50 Fosteum PLUS capsules. Those taking high doses of zinc-containing vitamins, cold medications, such as zinc lozenges, and some ophthalmic supplements for retinal diseases, should be monitored for zinc and copper status.

**CHOLECALCIFEROL**
There is limited information regarding acute vitamin $D_3$ toxicity in humans. The recommended upper limit for self-administration of cholecalciferol is 2,000 IU per day. Symptoms of vitamin D toxicity include hypercalcemia, hypercalciuria, anorexia, nausea, vomiting, polyuria, polydipsia, weakness and lethargy. Serum and urine calcium levels should be monitored in patients with suspected vitamin D toxicity.

## DOSAGE AND ADMINISTRATION
Fosteum PLUS should be taken twice a day, approximately 12 hours apart, and may be taken with or without food. Fosteum PLUS has no food limitations. There are no postural limitations.

## HOW SUPPLIED
Fosteum PLUS is a green and white capsule with "FOSTEUM PLUS" and "52011" printed on the body of the capsule.
They are supplied as follows:
68040-611-16 unit-of-use bottle of 60 capsules with desiccant (30-day supply)
68040-611-08 carton of 1 5-day sample blister pack (10 capsules total)

**Storage**
Store at room temperature 59°– 86°F (15°– 30°C). Protect from light and moisture. Store capsules in original bottle until usage. Keep out of reach of children.

Manufactured for:
Primus Pharmaceuticals, Inc.
Scottsdale, AZ 85253
www.primusrx.com

Manufactured by:
UST, LLC
Layton, UT 84041

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