**NUTRITION MAGNESIUM**

There is only about 25 grams of magnesium present in a 135 kilogram person. Over half is present in the bones and it acts in all cells of the soft tissue, where it plays an important role in protein synthesis.

More than 300 enzyme systems in the body require magnesium as a cofactor (Wacker & Paris 1968) and are involved in both aerobic and anaerobic energy generation. Magnesium plays an important role in glycolysis, either directly as an enzyme activator or as a part of the Magnesium Adenosine-5′-triphosphate (Mg-ATP) complex. Magnesium is required for mitochondria to carry out oxidative phosphorylation. It also plays a role in regulating potassium fluxes and in the metabolism of calcium. (Al-Ghamdi et al 1994, Classen 1984, Waterlow 1992) The human body contains about 760 mg of magnesium at birth and 25 g in adulthood. (Forbes 1987, Schroeder et al 1969, Widdowson et al 1951) Just over half the body’s magnesium is found in bone, where it forms a surface constituent of the hydroxyapatite mineral component, and a further third is found in muscles and soft tissues. (Heaton 1976, Webster 1987) The intracellular concentration is about ten times that of the extracellular fluid. (Australian Government, Dept Health and Aging 2005)

In adults eating conventional diets, the efficiency of absorption varies greatly with magnesium content (Seelig 1982, Spencer et al 1980) ranging from 25% on high magnesium diets in one study to 75% on low magnesium diets. (Schwartz et al 1984) The homeostatic capacity of the body to adapt to a wide range of intakes is thus high. (Abrams et al 1997, Sojka et al 1997)

Magnesium is absorbed in the duodenum and ileum by both active and passive processes (Greger et al 1981). High fibre intakes (40–50 g/day) lower the magnesium absorption, probably because of the magnesium-binding action of the phytate phosphorus associated with the fibre. (Kelsay et al 1979, McCance & Widdowson 1942) There is no consistent evidence that moderate increases in calcium, iron or manganese affect magnesium balance. (Abrams et al 1997, Andon et al 1996, Lonnerdal 1995, Sojka et al 1997) However, high intakes of zinc at 142 mg/day will reduce absorption. (Spencer et al 1994b) Protein may also influence magnesium absorption. When protein intake is less than 30 g/day (Hunt & Schofield 1969), magnesium absorption decreases. When protein intake is greater than 94 g/day, renal magnesium excretion may increase (Mahalko et al 1983), although adaptation may occur.

Benefits of Magnesium include the following:

- Energy production & cellular activity
- Metabolism of carbohydrates, fats & protein synthesis
- Neuromuscular transmission and nerve conduction
- Muscle activity and contraction and vascular tone in the body (supplementation with magnesium can assist in the relief and management of muscular aches, pains, cramps and spasms)
- Synthesis of nucleic acid and in the synthesis of RNA and replication of DNA
- Important constituent of the bones and supports the health and strength of bones, and vital in the maintenance of healthy bone density
- Involvement in the management of normal blood pressure
- Maintains the health of the cardiovascular system
- Immune function
The pathological effects of primary nutritional deficiency of magnesium are rare in humans, unless low intakes are accompanied by prolonged diarrhoea or excessive urinary loss. The body is generally protected by the lability of serum magnesium. Most of the early signs of deficiency are neurologic or neuromuscular defects (Shils 1969, 1988) that may develop with time into anorexia, nausea, muscular weakness, lethargy, weight loss, hyper-irritability, hyper-excitability, muscular spasms, tetany, and finally, convulsions.

Hypocalcaemia can occur in moderate to severe magnesium deficiency. Some studies have indicated that low magnesium status may be a risk for postmenopausal osteoporosis (Abraham & Grewal 1990, Reginster et al 1993, Stendig-Lindberg et al 1993, Tucker et al 1995, Yano et al 1985) however others have not confirmed the link. (Angus et al 1988, Freudenheim et al 1986) Sub-optimal magnesium status may be a factor in the aetiology of coronary heart disease and hypertension, but evidence is relatively sparse. (Elwood 1994) Magnesium depletion has been shown to cause insulin resistance and impaired insulin secretion (Paolissa et al 1990), and magnesium supplements have been reported to improve glucose tolerance and insulin response in the elderly. (Paolissa et al 1989, 1992)

Indicators used for estimating magnesium requirements have included serum magnesium, plasma ionised magnesium, intracellular magnesium, magnesium balance, estimates of tissue accretion in growth, magnesium tolerance tests and epidemiologic studies including meta-analysis. However, serum magnesium has not been properly validated as a reliable indicator of body magnesium status. (Gartside & Glueck 1995) Plasma ionised magnesium may be an improvement on serum magnesium but requires further evaluation and the validity of evidence for intracellular magnesium is limited. Magnesium balance is problematic if not carried out under close supervision, as magnesium in water can confound results, a factor that precluded the use of many early studies conducted in free-living situations or current studies where intakes were calculated, not analysed.

Accurate estimates of tissue accretion during growth throughout childhood are dependent on more extensive information about whole body mineral retention than are currently available, although there has been some older research on some information for specific ages from cadaver data. (Fomon & Nelson 1993, Koo & Tsang 1997) The magnesium tolerance test is an invasive procedure based on renal excretion, of a parentally administered magnesium load. It is considered accurate for adults but not for infants and children. (Gullestad et al 1992, Ryzen et al 1985) The test requires normal renal handling and may be unreliable in diabetics and drug or alcohol users. It may also be affected by ageing of kidney tissue. (Gullestad et al 1994) Epidemiological studies with meta-analysis may indicate relationships between magnesium intake and health outcomes. (Australian Government, Dept Health and Aging 2005)

CREATINE

The majority of creatine in the body is found in skeletal muscle, where its major role is in the production of energy. Creatine is converted to phosph-creatine which is then used to assist the Kreb’s Cycle in converting ADP to ATP. Thus supplementation can lead to an increase in athletic performance. Creatine also plays an important role in the brain, where it has shown to improve cognitive ability and help patients with some neurodegenerative diseases. (Osiecki 2007)

FUNCTIONS

The major function of Magnesium is to stabilise the structure of ATP in the ATP dependant enzyme reactions.

Magnesium balance is maintained largely by gastrointestinal absorption and renal excretion. Magnesium may be absorbed along the length of the small intestine, but most absorption occurs in the jejunum. As with other divalent cation minerals, the entry step of magnesium from the gut lumen occurs by
two mechanisms: a carrier facilitated process and simple diffusion. Maintenance of these two mechanisms depends on absorption, excretion, and transmembranous cation flux, rather than hormonal regulation. Once in the cells, magnesium is bound mainly to protein and energy rich phosphates.

The control of magnesium balance is governed by the kidneys, which conserve magnesium efficiently, particularly when intake is low. Supplementing a normal intake increases urinary excretion and the serum magnesium level remains normal. (Krause 2000)

Magnesium balance is maintained largely by gastrointestinal absorption and renal excretion. Magnesium may be absorbed along the length of the small intestine, but most absorption occurs in the jejunum. As with other divalent cation minerals, the entry step of magnesium from the gut lumen occurs by two mechanisms: a carrier facilitated process and simple diffusion. Maintenance of these constant values

The kidney regulates magnesium homeostasis through active re-absorption that is influenced by the sodium load in the tubules and possibly acid-base balance. (Quarme & Disks 1986) High dietary calcium intake (about 2,600 mg/day) with high sodium intake enhances magnesium output (Greger et al 1981), contributing to a shift to negative magnesium balance. (Kesteloot & Joosens 1990, Quarme et al 1986)

Magnesium is essential to many metabolic reactions, including lipid metabolism, amino acid activation, the glycolytic cycle, and the citric acid cycle. Its primary function is as an enzyme cofactor, thus producing energy, synthesizing lipids and proteins, regulating calcium flow and parathyroid hormone (PTH) secretion, forming urea, and relaxing muscles.

**Deficiency signs and symptoms – Magnesium**

- Muscle spasms
- Anorexia
- Nausea and vomiting
- Muscular weakness and spasm
- Lethargy
- Insomnia
- Depression
- Mental confusion and decreased attention span
- Personality changes
- Hyper-irritability and excitability
- Vertigo
- Cardiac arrhythmia, tetany and ultimately convulsions can develop if deficiency is prolonged.

Often magnesium deficiency is overlooked in a hospital setting (Braunwald et al 2003), with anywhere from 10-35% of people being admitted to hospital showing signs of possible magnesium deficiency. Braun 2007 reports on a study by Fox et al 2001, Guerrero-Romero & Rodriguez-Moran 2002 that clinically serious diseases such as congestive heart failure, ischemic heart disease, cardiac arrhythmias, hypertension, mitral valve prolapsed, metabolic syndrome, diabetes mellitus, hyperlipidaemia, pre-eclampsia and eclampsia may be associated with low levels of magnesium.

**Risk factors** that deplete magnesium include excessive intake of soft drinks, caffeine, salt and endocrine disorders such as hyperaldosteronism, hyperparathyroidism, hyperthyroidism and diabetes.

Prolonged stress may also heighten the likelihood of magnesium deficiency. Certain gastrointestinal disorders, such as inflammatory bowel diseases, celiac disease or prolonged vomiting and diarrhoea decrease absorption of magnesium.

**Cardiovascular System**

**Cardiovascular disease (CV)**

Magnesium has been used as a blood pressure lowering nutrient for decades. It was confirmed in a 2002 study (Jee et al 2002) in a meta-analysis involving 1220 subjects that
moderate doses of Magnesium reduce blood pressure. A reduction of 4.3 mmHg and of 2.3 mmHg in DBP was observed in those taking daily doses of 10 mmol.

Taking magnesium orally seems to reduce anginal attacks in people with coronary artery disease. There is some evidence that taking magnesium chloride and magnesium oxide orally can produce small decreases in low density lipoprotein (LDL) and total cholesterol levels, and small increases in high-density lipoprotein (HDL) levels. Potential benefits of magnesium supplementation thus include prevention of atherosclerosis and myocardial infarction, reduction of high blood pressure, treatment of angina, prevention of strokes, improvement of cholesterol and triglyceride levels, treatment of cardiac arrhythmia and treatment of congenital long QT syndrome (torsade de pointes).

**Cholesterol**
Magnesium supplementation can reduce vascular resistance, lower blood pressure and lead to more efficient heart function. Conditions which benefit from magnesium supplementation include cardiovascular disease, acute myocardial infarction, angina, cardiac arrhythmias, cardiomyopathy, congestive heart failure, high blood pressure. Magnesium is absolutely essential in the proper functioning of the entire cardiovascular system. Magnesium’s critical role in preventing heart disease and stroke is now widely accepted.

Low magnesium levels are associated with several cardiovascular diseases. The multiple biological effects of magnesium in the CV system suggest an important role in CV disease. In the heart, magnesium acts as a calcium channel blocker and promotes resting polarization of the cell membrane, thereby reducing arrhythmias. Calcium plays an important role in controlling the heartbeat, maintaining proper blood pressure and clotting blood. The importance of potassium's contribution to this function is best demonstrated by the consequences of elevations and depletions of potassium in extracellular fluid on cardiac function. Both conditions result in abnormal depolarization and repolarization of cardiac cells, leading to potentially fatal cardiac arrhythmias and conduction disturbances.

**Endocrine System**

**Premenstrual syndrome (PMS)**
Taking magnesium orally seems to relieve symptoms of PMS. There is some evidence that magnesium supplementation can improve symptoms including mood changes and fluid retention. Taking magnesium orally also seems to prevent premenstrual migraine. Reduced magnesium levels have been reported in women affected by PMS. An Italian double-blind randomized study in 32 women showed that a supplement of 360mg magnesium daily improved premenstrual symptoms related to mood changes. More recently, a randomised, double-blind, placebo-controlled study in 38 women showed no effect of magnesium supplementation (200mg daily) in the first month, but symptoms including weight gain, swelling of extremities, breast tenderness and abdominal bloating, improved during the second month. A further study in 44 women lasting 1 month showed that magnesium 200mg daily plus vitamin B650 mg daily produced a modest effect on anxiety-related premenstrual symptoms.

Magnesium deficiency is strongly implicated as a causative factor in PMS. Four independent studies have confirmed the observation of low RBC magnesium concentrations in PMS patients. One clinical trial of magnesium in PMS showed a reduction of nervousness in 89%, breast tenderness in 96% and weight gain in 95% of the women tested after magnesium supplementation. Oral magnesium supplementation decreases pain in premenstrual syndrome and the number of days with migraine headache according to one double-blind placebo controlled study on menstrual migraine headache. Two double blind studies using oral magnesium supplements in women with PMS have produced positive results for decreasing symptoms such as fluid retention and mood swings. A Cochrane review of the trial investigating the effects of various treatments for dysmenorrhoea found magnesium to be more effective than placebo for pain relief and resulted
in less extra medication being required. Magnesium supplements, at a dose of 200–400mg/day, may be helpful in relieving PMS symptoms and dysmennorhoea.

**Blood sugar regulation**
Plasma and intracellular magnesium concentrations are tightly regulated by several factors. Among them, insulin seems to be one of the most important. In vitro and in vivo studies have demonstrated that insulin may modulate the shift of magnesium from extracellular to intracellular space. Intracellular magnesium concentration has also been shown to modulate insulin actions (mainly oxidative glucose metabolism), offset calcium-related excitation–contraction coupling, and decrease smooth cell responsiveness to depolarizing stimuli. A poor intracellular magnesium concentration, as found in noninsulin-dependent diabetes mellitus (NIDDM) and in hypertensive patients, may result in a defective tyrosine-kinase activity at the insulin receptor level and exaggerated intracellular calcium concentration. Both events are responsible for the impairment in insulin action and a worsening in severity of insulin resistance in non insulin-dependent diabetic and hypertensive patients. By contrast, in NIDDM patients daily magnesium administration, restoring a more appropriate intracellular magnesium concentration contributes to improvement of insulin-mediated glucose uptake. The benefits deriving from daily magnesium supplementation in NIDDM patients are further supported by epidemiological studies showing that high daily intake of the mineral are predictive of a lower incidence of NIDDM. In conclusion, a growing body of studies suggest that intracellular magnesium may play a key role in modulating insulin-mediated glucose uptake and vascular tone. (Barbagallo et al 2003)

**Muscular-Skeletal System**

Preliminary evidence suggests that magnesium supplementation may prevent bone loss in postmenopausal osteoporosis. Magnesium is an important constituent of healthy bone, and supplementation has been shown to increase bone density in individuals with osteoporosis. Increased magnesium intake is associated with a lower decline in BMD after the menopause. Magnesium supplementation is as important as calcium supplementation in the treatment and prevention of osteoporosis. Magnesium is involved in a number of activities supporting bone strength, preservation and remodeling. Several studies have investigated the effects of magnesium on bone density, generally finding it has positive effects.

**Chronic Leg Cramps**
Evidence suggests that magnesium supplementation may help reduce pregnancy-related leg cramps. Oral magnesium supplements are used for conditions involving muscle spasm or tension and pain. Signs and symptoms of magnesium deficiency include problems in muscle contraction/relaxation and muscle cramps.

**Respiratory System**

**Asthma**
At a dose of 200mg daily for children aged 7 years and 290mg for those older it was shown (Mathew & Altura, 1988 in Braun 2007) “that magnesium is beneficial in the treatment of acute asthma as it may influence bronchial vasomotor tone, pulmonary vascular muscle contractibility, mast cell granulation and neurohumoral mediator release.” In these studies, infusion or inhalation methods have been used, however other studies (Bede et al 2003, Hill et al 1997 in Braun 2007) have shown that oral supplementation has resulted in an improvement of symptoms in mild to moderate persistent asthma.

**Nervous System**

Magnesium supplements have been used in a number of conditions, most notably muscle spasms, pain, psychological and physical symptoms of stress. There have been studies showing the effective use of magnesium with chronic fatigue syndrome, anxiety, ADHD, insomnia and tension headaches. Also Jacka et al (2009) the report showed that magnesium deficiency has been related to depression in community-dwelling adults such as elderly communities.

**Contraindications or Adverse Reactions**
Commonly oral supplementation may contribute to diarrhoea (18.6%) and gastric irritation (4.7%) (Peikert et al 1996) Braun reports that doses above 350mg
elemental magnesium per day may contribute to adverse effects.

Magnesium supplementation is contraindicated in renal failure. Hypermagnesaemia can develop in patients with renal failure particularly in combination with other medications.

**Interactions**

**Loop Diuretics:** Due to the kidney excretion, long term use of drugs of this nature may increase magnesium loss.

**Tetracycline and fluoroquinolone antibiotics:** this antibiotic will form insoluble complexes if taken with magnesium. They should be taken apart.

**Calcium channel blockers:** Magnesium supplementation should always be monitored in patients taking heart medications. In theory, they should complement each other however patients must be made aware of a possible hypotensive response to taking magnesium.

Many pharmaceutical drugs have potential to cause hypomagnesaemia (e.g. loop diuretics, corticosteroids, and antibiotics such as the aminoglycosides and tetracyclines.)

**CLINICAL APPLICATIONS**

Magnesium orotate is used as a nutritional supplement because its absorption is regarded as excellent. Orotic Acid may facilitate the transport of minerals into the bloodstream from the digestive tract. Some supplemental forms of minerals are therefore provided in forms that are bound to Orotic Acid, in order to enhance their bioavailability. Magnesium aspartate is comprised of 7.5% - 20% Magnesium bound to Aspartic Acid (Aspartate), and is also very well absorbed.

Dr Hans Nieper of Germany recognized that to deliver a mineral into a cell you must have good absorption, delivery and easy transport across the cell membrane and that by binding the mineral to a stable natural carrier substance, like an orotate or aspartate, this could be achieved. Some natural mineral carriers like citrates, lactates and gluconates are not pH stable and break down in the acidic environment of the stomach, releasing the mineral as a charged ion. Mineral transporters are attracted to certain tissues e.g. Orotates are taken up by bone, cartilage, liver, heart, blood brain barrier, blood vessels and Aspartates are taken up by muscles, heart, liver glands, breast tissue. Aspartates deliver minerals to the inner layer of the cell membrane.

Damaged liver and myocardial cells are low in magnesium and potassium, and potassium and magnesium aspartate have been shown to protect against heart and liver damage. Supplementation with these nutrients also results in an increase in muscular energy, greater muscle contraction, a faster reduction of lactic acid levels after exercise with associated faster recovery time.

Magnesium orotate and potassium and magnesium aspartate used together support and increase mitochondrial production of ATP and cellular energy. The heart gets 50% of its energy by metabolizing fatty acids and the mobilization of these fatty acids by enzymes is controlled by magnesium and calcium. Dr Neiper believed that supplementing with magnesium orotate over a period of 1-2 years results in a reduction in the calcified cholesterol plaques lining the blood vessels, as the magnesium orotate activates the cholesterol dissolving enzymes which mobilize the cholesterol away from the plaque, thus reducing arteriosclerosis and increasing cell wall elasticity. Magnesium orotates role in maintaining cardiac energy production is via the pentose phosphate pathway which is used by specialized muscle tissue for heart conduction.

Other than the importance of the Magnesium form, it is also important for the metabolism of other nutrients; (Braun & Cohan 2007)

- Calcium, also acting as a calcium antagonist and works with potassium, phosphorus, B6 and boron.
- Potassium
- Copper
- Zinc
- Sodium
- Phosphorus
- Thiamine

**Dose Range according to Australian and New Zealand Nutrient Reference Values (2005)**

**EAR = Estimated Average Requirement**

**RDI = Recommended Daily Intake**

**Infants**

0–6 months 30 mg/day
**7–12 months 75 mg/day**

**Rationale:** The average intake (AI) for 0–6 months was calculated by multiplying the average intake of breast milk (0.78 L/day) by the average concentration of magnesium in breast milk (34 mg/L) from 10 studies reviewed by Atkinson et al (1995), and rounding (FNB: IOM 1997). Magnesium is somewhat less bioavailable in formula based on cow’s milk but most formulas have higher magnesium content than found in human milk and should be adequate. The AI for 7–12 months was set by adding an estimate for magnesium from breast milk at this age to an estimate of intake from supplementary foods.

A breast milk volume of 0.6 L/day (Dewey et al 1984, Heinig et al 1993) and the average magnesium concentration of breast milk of 34 mg/L (Atkinson et al 1995) gives a contribution of 20 mg/day from breast milk which is added to 55 mg/day from complementary foods (Specker et al 1997).

<table>
<thead>
<tr>
<th>Children &amp; adolescents</th>
<th>EAR</th>
<th>RDI</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1–3 yr</td>
<td>65 mg/day</td>
<td>80 mg/day</td>
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<tr>
<td>4–8 yr</td>
<td>110 mg/day</td>
<td>130 mg/day</td>
</tr>
<tr>
<td>Boys</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9–13 yr</td>
<td>200 mg/day</td>
<td>240 mg/day</td>
</tr>
<tr>
<td>14–18 yr</td>
<td>340 mg/day</td>
<td>410 mg/day</td>
</tr>
<tr>
<td>Girls</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9–13 yr</td>
<td>200 mg/day</td>
<td>240 mg/day</td>
</tr>
<tr>
<td>14–18 yr</td>
<td>300 mg/day</td>
<td>360 mg/day</td>
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<table>
<thead>
<tr>
<th>Adults</th>
<th>EAR</th>
<th>RDI</th>
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<tbody>
<tr>
<td>Men</td>
<td></td>
<td></td>
</tr>
<tr>
<td>19–30 yr</td>
<td>330 mg/day</td>
<td>400 mg/day</td>
</tr>
<tr>
<td>31–50 yr</td>
<td>350 mg/day</td>
<td>420 mg/day</td>
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<tr>
<td>51–70 yr</td>
<td>350 mg/day</td>
<td>420 mg/day</td>
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<tr>
<td>&gt;70 yr</td>
<td>350 mg/day</td>
<td>420 mg/day</td>
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<tr>
<td>Women</td>
<td></td>
<td></td>
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<tr>
<td>19–30 yr</td>
<td>255 mg/day</td>
<td>310 mg/day</td>
</tr>
<tr>
<td>31–50 yr</td>
<td>265 mg/day</td>
<td>320 mg/day</td>
</tr>
<tr>
<td>51–70 yr</td>
<td>265 mg/day</td>
<td>320 mg/day</td>
</tr>
<tr>
<td>&gt;70 yr</td>
<td>265 mg/day</td>
<td>320 mg/day</td>
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<tr>
<th>Pregnancy</th>
<th>EAR</th>
<th>RDI</th>
</tr>
</thead>
<tbody>
<tr>
<td>14–18 yr</td>
<td>335 mg/day</td>
<td>400 mg/day</td>
</tr>
<tr>
<td>19–30 yr</td>
<td>290 mg/day</td>
<td>350 mg/day</td>
</tr>
<tr>
<td>31–50 yr</td>
<td>300 mg/day</td>
<td>360 mg/day</td>
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**Rationale:** As there are no direct studies of needs in pregnancy, the EARs and RDIs for pregnancy were based on a consideration of the added lean body mass in pregnancy, assumed to be a mean of 7.5 kg (IOM 1991), a magnesium content of the additional lean body mass of 470 mg (Widdowson & Dickerson 1964) and an adjustment factor of 2.5 for a bioavailability of 40% (Abrams et al 1997). This gives an additional requirement of 35 mg in pregnancy (FNB: IOM 1997) as estimated from (7.5 kg/270 days) x 470 mg/kg x 2.5 = 33 mg, rounded to 35 mg. A CV of 10% for the EAR was assumed to derive the RDI.
Dose by Condition:

Cardiovascular disease:
- Hypertension – 360-600 mg/day
- Mitral prolapsed – 600 mg/day (7mmol of elementary Mg)
- Coronary artery disease – 365 mg/day total magnesium

Migraine – 600mg daily, prophylaxis in children (9 mg/kg/day)

Premenstrual mood swings – 360 mg taken three times daily from mid cycle to menstrual flow.

Premenstrual fluid retention – 200mg daily

Nocturnal leg cramps – 300mg daily

Osteoporosis prevention – 250mg at night on an empty stomach, increasing to 250mg three times daily for 6 months, then only 250mg daily for 18 months.

Kidney stone prevention – 400-500mg daily

Asthma – 200-290mg daily

References are available by request.