Mag-Tab SR Caplets

Mag-Tab SR is indicated for the treatment of patients with, or at risk of magnesium deficiency. Magnesium deficiency can result from inadequate nutritional intake or absorption, magnesium depleting drugs, alcoholism. Certain diseases such as diabetes may also cause magnesium deficiency.

Each caplet shaped tablet contains:

DESCRIPTION

Mag-Tab SR contains Magnesium-L-lactate-dihydrate 84 mg or 7mEq of elemental magnesium

Inactive Ingredients:

Polyethylene glycol, microcrystalline cellulose, carnauba wax, stearic acid, calcium stearate, and D & C Yellow # 10.

Chemistry/Description

Magnesium L-lactate –dihydrate is a white crystalline powder that is soluble in water: one gram dissolves in 25 mL cold water, 3.5 mL boiling water; it is slightly soluble in alcohol. The aqueous solution is slightly acidic. (DMF)

Magnesium L-lactate is stable at room temperature, normal lighting and humidity. Mag-Tab SR caplets have expiration dates of at least 48 months when stored at recommended controlled room temperatures of 15° to 30° C (59° to 86° F).

The empirical formula is C6H10MgO6. 21-120 and the molecular weight is 238.48.

Figure1. Structural Formula

The Mag-Tab SR continuous release formulation provides maximum absorption and bioavailability at the pH of the ileum and jejunum where the majority of magnesium (Mg) is absorbed; and it minimizes the gastrointestinal side effects (e.g. cramping, diarrhea) seen with other formulations. The lactate anion is better absorbed than other Mg++ salts and it is not associated with a cathartic effect. (Somberg, Firoz, Data on File Niche). The formulation is a continuous release rather than an immediate release which improves the absorption process, and intraluminal concentrations of the released salt are kept to a minimum.

In addition, the continuous release formulation provides another important property. The transient rise of serum M++ after oral supplementation represents a pool of Mg available for redistribution into tissue. Renal excretion competes against tissue uptake for redistribution of serum Mg ++. The healthy kidney efficiently excretes excess Mg++. An immediate release formulation is associated with increased renal clearance relative to tissue redistribution because of a rapid influx of absorbed Mg++, leading to a spike in serum Mg++ concentrations. The Mag-Tab SR continuous release formulation facilitates a slower
absorption pattern, which enables tissue redistribution to compete more effectively against renal excretion.

PHARMACOLOGY

Magnesium is the fourth most abundant cation in the body and the second (after potassium) most abundant intracellular cation. Magnesium plays a critical role in a variety of cell functions and regulates many receptor systems that use adenosine triphosphate (ATP). It has been identified as a cofactor in over 300 enzymatic reactions involving energy metabolism and protein and nucleic acid synthesis. (2)

Magnesium (Mg++) is an essential factor in regulating ion transport in and out of cells, and stabilizes cell membrane permeability and electrolyte balance. Mg++ ions are a cofactor for the normal functioning of the ATP-dependent sodium-potassium "pump" found in muscle membrane. The efficiency of the pump is compromised without magnesium. A high frequency of hypomagnesemia occurs in concert with other electrolyte abnormalities. (see Figure Below) Many clinicians believe that hypomagnesemia is an important component of hypokalemia. (2) (5) Calcium is a direct antagonist of magnesium and hypercalcemia can lead to hypomagnesemia. (2) Magnesium opposes the entry of Ca++ into cells and blood vessel walls and serves as a "natural calcium channel blocker". (6)

Figure 2: Frequency of Low Mg++ Levels with Other Electrolyte Abnormalities.

Systemically, magnesium lowers blood pressure and alters peripheral resistance in patients with low serum Mg++ levels. (Reference) Mg++ homeostasis disturbances are fairly common in clinical practice, e.g., hypomagnesemia associated with patients receiving diuretic therapy, and diabetic patients whose disease causes glycosuria leading to significant renal magnesium wasting. (Reference Guerrero, others)

Pharmacokinetics

Magnesium balance is a function of intake and excretion. Magnesium absorption occurs primarily in the distal small intestine, (jejunum and ileum), although a small amount is absorbed in the colon. (1) Solubility and absorption of Mg++ across a range of pH's are necessary to correct deficiencies. (1,7, 8)

Normal individuals need to ingest 0.3 to 0.4 mEq /kg/d to stay in balance. Of the total amount ingested, approximately 30% to 40% is absorbed, primarily in the small bowel, through both a transport system and passive diffusion resulting from the bulk flow of water. Unlike calcium, there is no active transport
system for Mg++ re-absorption in the small intestine. Two other processes take place in the gut: Mg++ secretion of approximately 40 mg (1.7 mmol) in the intestinal secretions; and absorption of 20 mg (0.8 mmol) in the sigmoid colon. (2)

The kidney is the major regulator of serum magnesium levels. In the healthy adult, there is no net gain or loss of Mg++ from bone and the overall Mg balance is achieved by the urinary excretion of approximately 100 mg (4.1 mmol) or about one-third of what is absorbed. (5) Figure 3 below shows the distribution of Mg in the body.

Figure 3

![Figure 3: Distribution of Magnesium in the Body, includes Dietary Intake, GI Absorption and Urinary Excretion.](image)

While only 1% of body Mg++ is distributed extracellularly (which does not reflect intracellular levels), serum Mg++ levels should still be tested to detect cases of obvious magnesium deficiency. The normal range for serum Mg++ in adults is 1.6 to 2.5 mEq / d L (7)
Absorption:

Unlike other oral magnesium supplements with low or marginal solubility the Mag-Tab SR (magnesium L-lactate-dihydrate) formulation provides more soluble, absorbable and bioavailable Mg++ across a range of pH’s. (See Table 1)

Figure 5 show that serum Mg levels were significantly higher (p<0.05) in normal subjects after administration of Mag-Tab SR vs. Enteric coated magnesium chloride. (Reference Data on File Niche)
Distribution: Magnesium is distributed throughout the body with approximately one-half of the total Mg++ in soft tissue, the majority of the remaining Mg++ is in bone and less than 1% in the blood. Normal serum Mg concentrations range from 1.6 to 2.5 mEq/dL in adults, 1.6 to 2 mEq/dL in children and 1.6 to 2.3 mEq/dL in neonates and infants. (2)

Magnesium crosses the placenta and is excreted into breast milk; however, problems in humans have not been reported. Magnesium passes into spinal fluid at levels of 2.0 to 2.5 mEq/dL.

Metabolism /Excretion. Magnesium is not metabolized. The kidneys regulate elimination and the rate of excretion varies with the patient’s condition and level of hypo-, hyper-, or normomagnesemia. Eighty percent of plasma Mg++ is unbound and available for glomerular filtration. Under normal conditions, 95% of the filtered load is reabsorbed by the kidney and 5% (about 100 mg of total) appears in the urine. In clinical conditions of Mg++ deficiency, the kidney can decrease the amount excreted to less than 0.5% of the filtered load. Conversely, in conditions of hypermagnesemia or magnesium infusion, the kidney has the ability to increase the excretion of Mg ++ to 40% to 80% of the filtered load. (12)

Figure 6. Comparative Solubility of Magnesium Lactate and Magnesium Oxide

Table 1: Comparative Solubility of Mag-Tab SR and Magnesium Oxide. A comparative solubility experiment. (Data on file Niche, Lindberg)
### Table 1. Comparative Solubility of Magnesium Lactate and Magnesium Oxide.

<table>
<thead>
<tr>
<th>pH</th>
<th>L-lactate % W/W*</th>
<th>Oxide % W/W</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.2 (SGF)</td>
<td>93.6</td>
<td>14.1</td>
</tr>
<tr>
<td>2.2 (SGF)</td>
<td>82.7</td>
<td>0.058</td>
</tr>
<tr>
<td>3.9 (SGF)</td>
<td>80.9</td>
<td>0.016</td>
</tr>
<tr>
<td>5.5 (SIF)</td>
<td>84.8</td>
<td>0.001</td>
</tr>
<tr>
<td>6.8 (SIF)</td>
<td>85.0</td>
<td>0.001</td>
</tr>
<tr>
<td>7.5 (SIF)</td>
<td>78.3</td>
<td>0.001</td>
</tr>
<tr>
<td>9.0 (SIF)</td>
<td>83.2</td>
<td>0.001</td>
</tr>
</tbody>
</table>

* Weight/Weight

### Table 2.1. Serum magnesium comparisons of Mag-Tab SR caplets after dosing (Day 3) vs. prior to dosing (Day 2); N=24.

<table>
<thead>
<tr>
<th>Least Squares Means</th>
<th>Day 3</th>
<th>Day 2</th>
<th>Observed Difference (%)</th>
<th>Power</th>
<th>99% Confidence Interval (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC (mEq hr/L)</td>
<td>45.22</td>
<td>41.78</td>
<td>8.22**</td>
<td>&gt;0.99</td>
<td>7.6 8.9</td>
</tr>
<tr>
<td>Cmax (mEq/L)</td>
<td>1.99</td>
<td>1.64</td>
<td>8.09**</td>
<td>&gt;0.99</td>
<td>6.9 9.3</td>
</tr>
<tr>
<td>Tmax* (hours)</td>
<td>8.08</td>
<td>8.33</td>
<td>-3.00</td>
<td>0.18</td>
<td>-   -</td>
</tr>
</tbody>
</table>

* Time after most recent dose.
**Detected as statistically significant by ANOVA at the p<0.05 level.

### Table 2.2. Urine magnesium comparisons of Mag-Tab SR caplets after dosing (Day 3) vs. prior to dosing (Day 2); N=24.

<table>
<thead>
<tr>
<th>Least Squares Means</th>
<th>Day 3</th>
<th>Day 2</th>
<th>Observed Difference (%)</th>
<th>Power</th>
<th>99% Confidence Interval (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CUE 0-24 (MG)</td>
<td>12.18</td>
<td>8.67</td>
<td>40.52**</td>
<td>0.92</td>
<td>30.7 50.3</td>
</tr>
</tbody>
</table>

**Detected as statistically significant by ANOVA at the p<0.05 level.

### Table 2.3. Urine magnesium comparisons of Mag-Tab SR caplets on the day after dosing (Day 4) vs. prior to dosing (Day 2); N=24.

<table>
<thead>
<tr>
<th>Least Squares Means</th>
<th>Day 4</th>
<th>Day 2</th>
<th>Observed Difference (%)</th>
<th>Power</th>
<th>99% Confidence Interval (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CUE 0-24 (MG)</td>
<td>11.51</td>
<td>8.67</td>
<td>32.74**</td>
<td>0.92</td>
<td>22.9 42.6</td>
</tr>
</tbody>
</table>

**Detected as statistically significant by ANOVA at the p<0.05 level.**
Comparative Study: Mag-Tab SR vs. Slow Mag

Comparative Study: Magnesium-L-lactate dihydrate Bioavailability Not Impaired by Decreased Gastric Activity.

Table #3 AUC Comparison magnesium lactate vs. magnesium chloride

<table>
<thead>
<tr>
<th>Treatment</th>
<th>lm-g/h/1L</th>
<th>T-max</th>
<th>Emesis</th>
<th>Diarrhea</th>
</tr>
</thead>
<tbody>
<tr>
<td>MgCl₂</td>
<td>9</td>
<td>8 h</td>
<td>1/12</td>
<td>5/12</td>
</tr>
<tr>
<td>MgCl₂ + Ranitidine</td>
<td>11</td>
<td>4 h</td>
<td>2/12</td>
<td>2/12</td>
</tr>
<tr>
<td>Mg Lactate</td>
<td>15*</td>
<td>4 h</td>
<td>1/12</td>
<td>3/12</td>
</tr>
<tr>
<td>Mg Lactate + Ranitidine</td>
<td>17*</td>
<td>4 h</td>
<td>1/12</td>
<td>1/12</td>
</tr>
</tbody>
</table>

*Significantly (p<0.05) greater than corresponding MgCl₂ value.

Table 4. Comparison of Magnesium Products’ Solubility, Absorption and Bioavailability (Niche data, Somberg, and Firoz)

<table>
<thead>
<tr>
<th>Product</th>
<th>Mag-Tab SR</th>
<th>Slow-Mag*</th>
<th>Magnenate*</th>
<th>MagOx® 400</th>
</tr>
</thead>
<tbody>
<tr>
<td>Form of magnesium</td>
<td>L-lactate</td>
<td>Chloride</td>
<td>Gluconate</td>
<td>Oxide</td>
</tr>
<tr>
<td>Elemental Mg²⁺/dose</td>
<td>84 mg</td>
<td>64 mg</td>
<td>27 mg</td>
<td>241 mg</td>
</tr>
<tr>
<td>mEq Mg²⁺ per dose</td>
<td>7 mEq</td>
<td>5.26 mEq</td>
<td>2.2 mEq</td>
<td>19.8 mEq</td>
</tr>
<tr>
<td>Solubility</td>
<td>Excellent</td>
<td>High</td>
<td>Moderate</td>
<td>Extremely low</td>
</tr>
<tr>
<td>Oral Absorption</td>
<td>41.1%</td>
<td>19.68%</td>
<td>19.25%</td>
<td>2.00%</td>
</tr>
<tr>
<td>Bioavailable (bio) mEq Mg²⁺ per dose</td>
<td>2.87 mEq</td>
<td>1.04 mEq</td>
<td>0.42 mEq</td>
<td>0.39 mEq</td>
</tr>
</tbody>
</table>

Warning/Contraindications:
Patients with renal disease should not ingest magnesium containing formulations without the advice and direct supervision of their physician. Magnesium formulations are contraindicated in patients with GI obstruction and ileus. See Section V for Drug Interactions and additional information.

INDICATION AND USAGE:
Mag-Tab SR is an orally administered dietary supplement specially formulated and indicated for the dietary management of suboptimal magnesium levels caused by glycosuria in diabetic patients and in cardiovascular patients receiving chronic diuretic therapy.

Safety Profile, Tolerability, Warnings/Contraindications.
Patients with renal disease should not take Mag-Tab SR without the advice and direct supervision of their physician. While there are no contraindications to MLD09, it should not be prescribed to patients with existing hypermagnesemia. Also some clinicians suggest that when used as laxatives, magnesium supplements are contraindicated in patients with GI obstruction and ileus. (Note: MLD09 is not a laxative; and the unique lactate formulation produces a low incidence of GI distress or diarrhea. To date, placebo controlled trials of Mag-Tab SR (magnesium-L-lactate –dihydrate) report an incidence of GI side effects no greater than placebo. (McBride and Niche Data).

Magnesium salts should be used with caution in dehydrated patients, since continued administration may lead to severe dehydration due to fluid loss via the GI tract.

Oral magnesium salts are classified pregnancy category B; and oral Mg++ salts are distributed into breast milk. Problems with Mag-Tab SR in pregnancy have not been demonstrated with normal daily recommended dosages. One study in France of 22 pregnant women receiving 2 g/day of magnesium lactate for one month reported no mention of any symptoms of intolerance. (reference Dumont) IV magnesium has long been the standard of care for pregnant women with eclampsia and no adverse effects have been reported in the medical literature. (Reference)

Drug Interactions: Serious problems with drug interactions have not been noted with Mag-Tab SR. However, some sources caution about the drug interactions listed in Table 5, which are especially important in patients receiving magnesium sulfate and other magnesium salts administered parenterally.

Table 5: Reported Drug Interactions with IV Magnesium. (Reference)
The concurrent use of oral Mg++ salts with sodium polystyrene sulfonate is not recommended since it may bind with oral Mg++ salts.

Excessive intake of ethanol or glucose has been found to increase Mg++ excretion. High intake of ethanol or glucose should be avoided while taking Mg++ salts.

Oral calcium-containing medications may increase serum Ca ++ or Mg++ concentrations in susceptible patients, primarily patients with renal insufficiency.

Administration of oral Mg salts with cellulose sodium phosphate or edetate disodium (EDTA) may result in binding of Mg++. Do not administer oral Mg salts within one hour of cellulose sodium phosphate or edetate disodium.

Diuretics may interfere with the kidneys ability to regulate Mg++ levels. Long-term use of PPI’S, thiazide or loop diuretics may impair the magnesium-conserving ability of the kidneys and lead to hypomagnesemia.

Concurrent use of Mg++ salts with other magnesium-containing antacids or laxatives may result in magnesium toxicity, especially in patients with renal insufficiency.

Administration of oral Mg ++ salts with oral quinolones or tetracycline antibiotics may form nonabsorbable complexes resulting in decreased absorption of the antibiotics. Do not administer oral Mg++ salts within 1 to 3 hours after taking an oral fluoroquinolone or oral tetracycline.(reference)

Oral Mg salts may prevent absorption of oral etidronate. Do not administer Mg++ salts within 2 hours of oral etidronate.

<table>
<thead>
<tr>
<th>Antacids</th>
<th>Antidepressants</th>
</tr>
</thead>
<tbody>
<tr>
<td>Barbiturates</td>
<td>Benzodiazepines</td>
</tr>
<tr>
<td>Calcium Salts</td>
<td>Cardiac glycosides</td>
</tr>
<tr>
<td>Cellulose Sodium Phosphate</td>
<td>Diuretics</td>
</tr>
<tr>
<td>Edetate Disodium, Disodium EDTA</td>
<td>Ethanol</td>
</tr>
<tr>
<td>Etidronate</td>
<td>General Anesthesia</td>
</tr>
<tr>
<td>H2-blockers</td>
<td>Laxatives</td>
</tr>
<tr>
<td>Local Anesthetics</td>
<td>Neuromuscular blockers</td>
</tr>
<tr>
<td>Nifedipine</td>
<td>Opiate agonists</td>
</tr>
<tr>
<td>Phenothiazines</td>
<td>Sodium Polystyrene Sulfonate</td>
</tr>
<tr>
<td>Quinolones</td>
<td>Tetracyclines</td>
</tr>
<tr>
<td>Vitamin D analogs</td>
<td></td>
</tr>
</tbody>
</table>
Magnesium salts and magnesium-containing antacids should not be used in patients receiving vitamin D analogs. Vitamin D analogs can increase serum Mg++ concentrations in patients with chronic renal failure.

Adverse Reactions: The most common side effects with oral magnesium salts are loose stools and diarrhea.

Tolerability: Mag-tab SR is generally well-tolerated and no serious adverse reactions have been reported. In well controlled double-blind, placebo controlled studies that employed up to 42 mEq’s of magnesium –L-lactate dihydrate in sick cardiac patients, side effects including loose stools and diarrhea occurred no more often than placebo. (McBride, Niche Data) Hypermagnesemia would be classified as:

- Toxic Serum Levels: > 5 mEq/L magnesium
- Toxic Serum Levels: > 12 mEq/L lactate
- Lethal serum levels: - 25 mEq/L magnesium

A number of studies in the USA and Europe have demonstrated the safety of magnesium lactate. In one study, subjects received 3 g/day for 30 days, followed by 1.5 g/day for at least another two months. Tolerance was described as "usually perfect." Another study of 40 subjects following the same dosage regimen reported excellent tolerance in all but one subject. (references)

In a study of 22 subjects treated with 3 g/day for six months, no intolerance was reported. A second study evaluated long-term magnesium lactate supplementation in 82 subjects reporting only minimal side effects: headache in one subject and diarrhea in another. (Dumont, Steidl)

A recent double-blind study found that chronic oral administration of magnesium lactate, amounting to 12 mmol daily for one month, was well-tolerated in thirty healthy volunteers. (18)

Mag-Tab SR contains L-lactate as the anion. The levoratory (L-) lactate salts are more soluble and better tolerated than the dextrorotary (D-) and racemic (DL-) salts. (19)

Lactate, or lactic acid, is a normal constituent of the body. It is produced during glucogenesis by active skeletal muscle and erythrocytes. The lactate formed by the active muscle through a series of chemical reactions is converted into glucose by the liver.

The daily lactate turnover in man is 2 grams per kilogram of body weight, or on the order of 120 to 140 grams daily. Two to four tablets of MLD09 will add 1.246 to 2.492 grams of lactate daily - a negligible addition to the physiologic load that is normally handled daily. Although human studies defining a maximum lactate load are not available, on the basis of utilization of lactic acid in intermediary metabolism it has been concluded that the acceptable daily lactate intake need not be limited. (3)

Concerning Lactose: Some patients and clinicians have mistakenly been concerned about lactose intolerance with MLD09. There is no chemical relationship between lactate and lactose. Lactose is a disaccharide composed of glucose and galactose. The intolerance to lactose is due to the deficiency of the enzyme, lactase. In patients with this deficiency, lactose accumulates in the lumen of the small intestine because there is no mechanism for the absorption of the disaccharide. The large osmotic effect of the unabsorbed lactose leads to an influx of fluid into the small intestine, which leads to the clinical symptoms. (Reference)
As noted previously, lactate (or lactic acid) is produced during gluconeogenesis by active skeletal muscle and erythrocytes and is a normal body constituent. The lactate is then converted by the enzyme lactic dehydrogenase into glucose by the liver.

Lactose is not used in the manufacture of Mag-Tab SR and there should be no problem with patients with lactose intolerance consuming Mag-Tab SR.

Dosage and Now Supplied

Under the recent Dietary Reference Intakes (DRIs), the revised dietary allowance (RDA) of magnesium for nutritional supplementation in healthy individuals is:

- Adult females, ages 19 to 30:
- Adult females during pregnancy:
- Adult females less than age 31:
- Adult males, ages 19 to 30:
- Adult males, less than age 31:
- Children 9-13 years of age:
- Children 4-8 years of age:
- Children 1-3 years of age:

Dosing: The usual dosage for adults is 1 or 2 tablets every 12 hours or as directed by your physician.

Where magnesium-depleting drugs are being used, supplementation with higher dosages may be required and should be considered. (2)

In a recent review article, nephrologists noted that because of the manner in which the kidney regulates Mg++, abrupt elevation in plasma Mg concentration will partially remove the stimulus to Mg++ retention, resulting in up to 50% of the infused Mg++ being excreted in the urine. They’ve observed that uptake by the cells is slow and that repletion of intracellular stores requires continuous correction of the hypomagnesemia. (2)

They conclude that the asymptomatic patient or the patient with chronic hypomagnesemia should be treated with an oral continuous release preparation (i.e., Mag-Tab SR). These clinicians recommend 40-50 mEq of Mag-Tab SR daily, taken in divided doses, for severe Mg++ depletion; and suggest 20 to 40 MEq of Mag-Tab SR daily for mild, asymptomatic disease. (2)

How Supplied. Mag-Tab SR caplets are available as oval shaped tablets. Each caplet contains 7mEq (84 mg) magnesium L-lactate dihydrate in a continuous release formulation.

Mag-tab SR caplets are available as:
- Bottles of 60
- Bottles of 100
- Bottles of 1000
- Unit dose Boxes of 100
References

1. Hardwick LL: JNutrl991; 121; 13-23
3. Data on File, Niche Pharmaceuticals , Inc.
11. Comparative Solubility Study: Part of the Information to Establish Safety and Functionality of Magnesium L-Lactate submitted to FDA; Niche Notebook #2241, pages 54-57.
15. Linberg JS: J Amer Coll Nutr 1990; (1) 48-55.