## Product Information

**LIMBREL®**
flavocoxid™ capsules by oral administration. **Dispensed by prescription.**
(U.S. patents 7,108,868 and 7,192,611; other patents pending.)

*A specially formulated medical food product, consisting primarily of a proprietary blend of flavonoid (polyphenol) ingredients, for the clinical dietary management of the metabolic processes of osteoarthritis (OA).* ***Must be administered under physician supervision.***

## OSTEOARTHRITIS (OA)

### OA as a Metabolic Deficiency Disease

Metabolic processes are important in the progression of OA. After initial damage to the joint due to trauma, overuse, or genetic factors, a cascade of inflammation, triggered by the release of cytokines (e.g., TNF$\alpha$, IL-$\beta$, IL-6), begins the development of OA. These cytokines up-regulate the expression of COX-2 (cyclooxygenase-2) and 5-LOX (5-lipoxygenase) enzymes, which metabolize fatty acids in the joint. This process is both enzymatic as well as oxidative, and occurs at a cellular level where the essential fatty acid, arachidonic acid (AA), is converted into various inflammatory products. With age, elevated levels of AA accumulate both from the diet and increased conversion of phospholipids produced by further damage to cells in the joint. Therefore, OA is sustained by imbalanced AA metabolism. Managing AA metabolism benefits OA patients by decreasing the damaging, metabolic inflammatory processes in the joint to improve functional mobility, reduce stiffness, and decrease joint discomfort.

When joint damage occurs, phospholipids released from damaged cell membranes are converted to AA. Enzymatic breakdown of AA then generates fatty acid metabolites that are involved in platelet aggregation, maintenance of stomach mucosa, organ function, proper blood flow, urine production, blood pressure, viral immunity, bone turnover and tissue repair. AA is metabolized via the COX (COX-1 & COX-2) and LOX (5-LOX) pathways to thromboxanes, prostaglandins, prostacyclins, and leukotrienes. Balanced AA metabolism by COX-1 and COX-2 is essential to sustain proper levels of critical regulators for renal and cardiovascular function maintained by thromboxanes (vasoconstrictors) and prostacyclins (vasodilators). An imbalance of these metabolites can result in high blood pressure, peripheral edema and, in severe cases, myocardial infarction. AA, metabolized by 5-LOX, produces leukotrienes (particularly $LTB_4$), that are strong chemoattractant molecules responsible for the migration of white blood cells (WBCs) to the site of injury. WBCs attracted to the joint by leukotrienes release histamines, produce reactive oxygen species (ROS) and cytokines, triggering additional inflammatory processes not treated by traditional non-steroidal anti-inflammatory drugs (NSAIDs) or selective COX-2 inhibitors. Inhibition of either or both COX-1 and COX-2 has been shown to shunt AA metabolism down the 5-LOX pathway, thereby potentially increasing, rather than reducing, inflammation in cartilage. In addition, AA is converted via an oxidative mechanism mediated by reactive oxygen species (ROS) to the oxidized lipids F2-isoprostanes, malondialdehyde, and 4-hydroxynonenal that directly degrade cartilage and induce production of other inflammatory proteins.

## DESCRIPTION

### Primary Ingredients

LIMBREL (flavocoxid) consists of a proprietary blend of two types of flavonoids, Free-B-Ring flavonoids and flavans, from *Scutellaria baicalensis* and *Acacia catechu*, respectively. These ingredients in LIMBREL are Generally Recognized As Safe (GRAS). For an ingredient to be recognized as GRAS, it 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. Many ingredients have been determined by the U.S. Food and Drug Administration (FDA) to be GRAS, and are listed as such by regulation, in Volume 21 Code of Federal Regulations (CFR) Sections 182, 184, and 186. Other ingredients may achieve "self-affirmed" GRAS status via a panel of experts in the pertinent field who co-author a GRAS Report. Finally, the FDA has specifically permitted a few ingredients as safe medical foods ingredients in Volume 21 CFR Section 172.345(f).

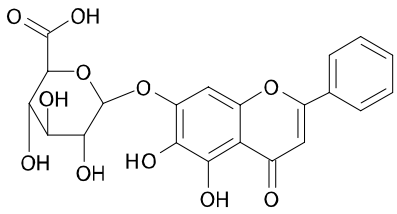
### Flavonoids

Flavonoids are a group of phytochemical compounds found in all vascular plants, including fruits and vegetables. They are a part of a larger class of compounds known as polyphenols. Many of the therapeutic or health benefits of colored fruits and vegetables, red wine, and green tea are directly related to their flavonoid content.

The specially formulated flavonoids found in LIMBREL, or their related compounds (i.e., other flavonoids, anthocyanins), cannot be obtained from conventional foods in the normal American diet at the same level as found in LIMBREL. This quantity of daily flavonoid intake generally would need to be significantly greater for patients with hypochlorhydria or low intrinsic factor, both of which occur most often in the elderly population. OA may not be managed simply by a change to the normal diet due to the high volume of vegetable and fruit matter that would need to be consumed.

#### *Baicalin*

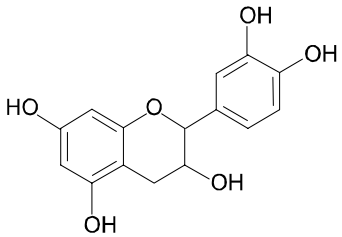
The primary Free-B-Ring flavonoid is baicalin (5,6,7-trihydroxyflavone,7-O-β-D-glucuronopyranoside), derived from the phytochemical food source material *Scutellaria baicalensis*, with a molecular weight of 446.37. Its molecular formula is C21H18O11, with the following chemical structure:




**Baicalin**

#### *Catechin*

The primary flavan is composed of catechin (3,3',4',5,7-pentahydroxyflavan (2R,3S form)), and its stereo-isomer, epicatechin (3,3',4',5,7-pentahydroxyflavan (2R,3R form)) from the phytochemical food source material *Acacia catechu* with a molecular weight of 290.27. Its molecular formula is $C_{15}H_{14}O_6$, with the following chemical structure:




**Catechin**

**Other Ingredients**
LIMBREL contains the following “inactive” or other ingredients as fillers, excipients, and colorings: magnesium stearate, microcrystalline cellulose, Maltodextrin NF, gelatin (as the capsule material), titanium dioxide, FD&C Blue #1, and FD&C Green #3. Capsules do not contain fructose, glucose, sucrose, lactose, gluten or flavors.

**Medical Foods**
Medical food products are often used in hospitals (e.g., for burn victims or kidney dialysis patients) and outside of a hospital setting under a physician’s care (e.g., for PKU, AIDS patients, cardiovascular disease, osteoporosis) for the dietary management of diseases in patients with particular medical or metabolic needs due to their disease or condition. 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 [or orally] 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.”[1] LIMBREL has been developed, manufactured, and labeled in accordance with both the statutory and the FDA regulatory definition of a medical food. LIMBREL is to be used under a physician's supervision.

[1]US Congress, 100th Congress Orphan Drug Act Amendment; 1988. 21 USC § 360ee(b)(3). And later incorporated into FDA's nutrition information regulation, Volume 21 CFR § 101.9(j)(8)(i)-(v).

**Physical Description**
LIMBREL is a yellow to light brown powder. It is partially soluble in water and glycerol, soluble in ethanol, methanol, and acetonitrile. It is practically insoluble in hexane. Each capsule of LIMBREL contains 250 mg or 500 mg of flavocoxid, as noted in the Primary Ingredients Section.

**CLINICAL PHARMACOLOGY**
**Mechanism of Action**
LIMBREL acts on COX-1, COX-2 and 5-LOX pathways. LIMBREL is NOT selective for either COX-1 or COX-2 enzymes. LIMBREL acts by restoring and maintaining the balance of fatty acids in OA. LIMBREL dampens AA metabolism at relatively equal levels in the COX pathway (mediated by conversion of AA via the COX-1 & COX-2 enzymes), as well as inhibiting the metabolism of AA by the 5-LOX enzyme. This balanced inhibition of metabolism in the COX pathway yields relatively equal levels of thromboxanes, prostaglandins, and prostacyclins that are key mediators of systemic organ function. Inhibition of these mediators in the COX pathway, in conjunction with inhibition of leukotrienes in the LOX pathway, results in a “dual inhibition” mechanism that manages inflammation with minimal effects on organ function. Inhibition of 5-LOX has been shown in cell-based assays to reduce the production of $LTB_4$, an agent that fosters WBC chemotaxis and the subsequent release of histamines, ROS, and pro-inflammatory cytokines. In addition, direct inhibition of the 5-LOX enzyme has been observed in enzymatic assays. This balanced down-regulation of these enzymatic pathways is relatively weak when compared to the effects of traditional NSAIDs and selective COX-2 inhibitors, thus allowing

the body to produce AA metabolites at relatively equal levels to maintain physiologic function.

LIMBREL also acts as a strong antioxidant to limit the oxidative conversion of AA by ROS to other damaging fatty acid products including hydroxyl radicals, superoxide anion radicals and hydrogen peroxide. LIMBREL has demonstrated an oxygen radical absorbance capacity (ORAC) of 5,517 μmolTE/g, as compared to Vitamin E (1,100 μmolTE/g) and Vitamin C (5,000 μmolTE/g).

Through these enzyme inhibition and antioxidant mechanisms, LIMBREL is beneficial for the clinical dietary management of the metabolic aspects of osteoarthritis. Inflammation, joint discomfort, and reduced flexibility are shown in published studies to be clinical manifestations of OA. At a biochemical and metabolic level, inflammation is not simply a marker of the disease process, but also plays an important role in OA progression. Chronic inflammation with elevated metabolic production of inflammatory metabolites has an etiological role in the progression of OA. Thus, successful dietary management of the metabolic processes of OA, results in a reduction of its characteristic inflammation by correcting OA's distinctive imbalance in AA metabolism.

**Hepatic, Renal, and Gastrointestinal Histology**

LIMBREL's effect on hepatic, renal, gastric, and duodenal tissue histology was tested in four animal toxicity studies; two for acute use and two for sub- chronic use.

In the acute use studies, healthy juvenile male and female mice received a 2,000 mg/kg oral dose (10,000 mg per day human equivalent, or at least 10 times the recommended human use of 500 - 1,000 mg per day) or placebo daily for 14 days. In two different sub-chronic use studies, three groups of healthy adult male and female mice consumed either 50 mg, 250 mg or 500 mg/kg doses (250 mg, 1,250 mg and 2,500 mg per day human equivalent) for 28 and 91 days respectively.

In all studies, the test subjects were evaluated relative to placebo control groups of healthy subjects with similar ages and sexes. Observations across all groups revealed no organ or behavioral abnormalities, nor differences in weight gain. Neither study showed changes in hepatic, renal, gastric, or duodenal histology. Blood electrolytes were unchanged, and liver enzyme levels and markers of renal function were all within normal limits.

**Food Effects**

LIMBREL is safe taken with or without other foods. Taking LIMBREL one hour before or after meals may help to increase the absorption of LIMBREL's key ingredients. This observation is based upon a pharmacokinetic study in humans, as well as in-market clinical experience in analyzing physician and patient product reports. Food does not affect the metabolism of LIMBREL and may buffer effects of slight indigestion.

**Metabolism**

LIMBREL is primarily carried bound to albumin in the blood and only a minor amount (<10%) is metabolized via glucuronidation and sulfation by hepatic metabolism involving cytochrome P450 isoenzymes (CYP). A primary ingredient constituent, baicalin, undergoes hydrolysis of the glucuronide moiety in the upper intestine via the action of intestinal flora and is absorbed

as the aglycone, baicalein. Glucuronidation and sulfation of baicalein occurs intra-hepatically. *In vitro* CYP assays using a microsomal enzyme system demonstrated minimal CYP inhibition (see below).

**Drug Interactions**

*In vitro* studies indicated that LIMBREL is not a significant inhibitor of cytochrome P450 1A2, 2C9, 2C19, 2D6, or 3A4. These isoenzymes are principally responsible for 95% of all detoxification of drugs, with CYP3A4 being responsible for detoxification of approximately 50% of drugs. Based on the results of this assay, LIMBREL does not appear to have a pronounced effect on drug metabolizing enzymes.

LIMBREL was tested at a 10 μM concentration in human recombinant (sf9 cells) using spectrophotometric quantization of 7-benzyloxy-4-(trifluoromethyl)-coumarin as substrate. In this test model, if inhibition does not reach at least 50% at 10 μM, CYP inhibition is considered to be insignificant and no further development of titration curves is deemed necessary. Inhibition by LIMBREL ranged from 11% inhibition to 23% inhibition of selected isozymes when studied at a 10 μM concentration**.** LIMBREL, therefore, does not appear to have a pronounced effect on the inhibition of hepatic drug metabolizing enzymes based on this 10 μM concentration. The data for CYP inhibition is shown below:

**Table 1. Cytochrome P450 Assay**

| CYP Isoenzyme | % Inhibition by LIMBREL |
|---|---|
| 1A2 | 23% |
| 2C9 | 11% |
| 2C19 | 16% |
| 2D6 | 15% |
| 3A4 | 11% |

**CLINICAL EXPERIENCE**

LIMBREL has demonstrated significant functional improvements when used for the clinical dietary management of the metabolic processes of OA.

**Double-blind, Randomized Clinical Efficacy Study vs. Naproxen**

LIMBREL was evaluated in a double-blind, randomized, active comparator (naproxen) controlled clinical study that enrolled 103 subjects with moderate or moderate-severe OA of the knee. Subjects were randomly assigned to receive either LIMBREL (500 mg BID) or naproxen (500 mg BID) for 4 weeks. Primary endpoints were the short WOMAC composite index (Western Ontario and McMaster Universities Osteoarthritis Index), investigator VAS for global response, subject VAS scales for global response and discomfort. Subjects were sex-matched and recruited from ages 35 to 85 years with an average age of 57-60 years per arm. There were no differences in demographic characteristics or in baseline WOMAC or VAS scores between the two arms. Subjects taking NSAIDs and/or gastroprotective medication underwent a 2-week washout period before beginning the trial. Subject activity

was not restricted, and subjects were free to withdraw from the trial at any time for any reason. Dropouts were minimal in both arms. Two subjects, one from each arm, failed to complete the trial for personal reasons unrelated to the study.

In this study, both LIMBREL and naproxen arms noted significant reduction in the signs and symptoms of knee OA. All within-arm improvements in efficacy endpoints were statistically significant (p≤0.001). The LIMBREL and naproxen arms performed nearly identically, and the between group differences were not statistically significant for any efficacy endpoint. See Figures 1-4 below for efficacy results of LIMBREL vs. naproxen in this study.

**Figure 1. Improvement in WOMAC***

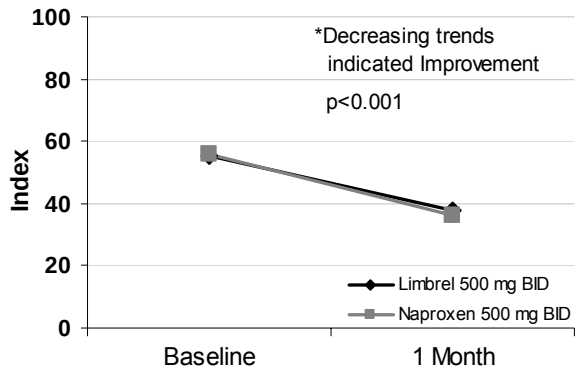



**Figure 2. Improvement in Physician VAS (Global Disease Assessment)****

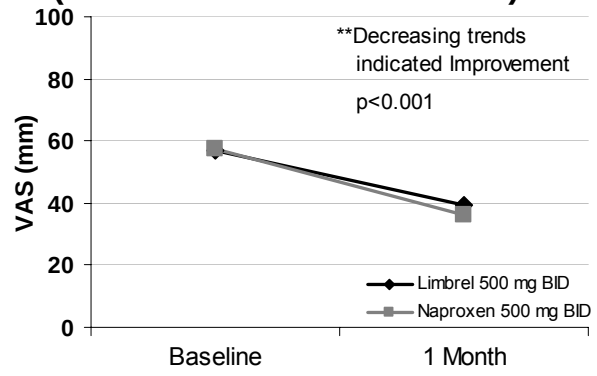



**Figure 3. Improvement in Subject VAS (Global Disease Assessment)†**

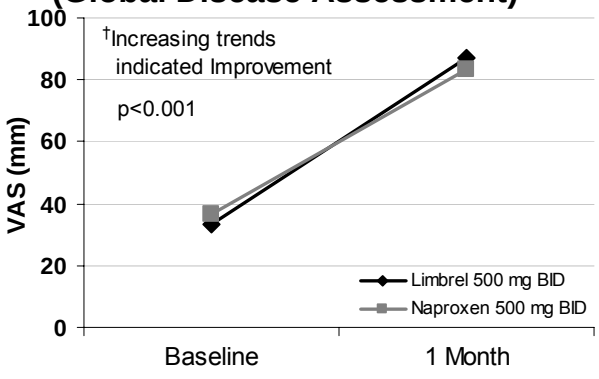
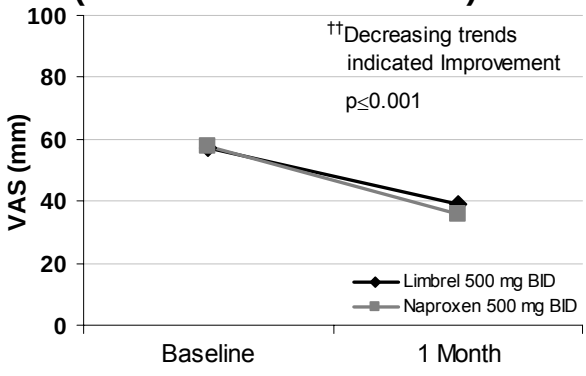



**Figure 4. Improvement in Subject VAS (Discomfort Assessment) ††**




Fisher's exact test was computed for improved vs. not improved (sum of unchanged and worsened) for all parameters (see Table 2). Both arms had a large percentage of subjects with significant improvement (75% to 88%). Differences were not significant between arms for percent of patients with improvement. There was a slight, non-significant trend toward greater improvement in physician global disease assessment VAS in the LIMBREL arm and WOMAC in the naproxen arm.

**Table 2. Percent of OA Patients with Improvement**

| | LIMBREL 500 mg BID (N=52) | Naproxen 500 mg BID (N=51) | p-value |
|---|---|---|---|
| WOMAC | 79% | 88% | <0.001 |
| Physician VAS (global disease assessment) | 83% | 75% | <0.001 |
| Subject VAS (global disease assessment) | 87% | 88% | <0.001 |
| Subject VAS (discomfort assessment) | 87% | 88% | ≤0.001 |

**Double-blind, Randomized Clinical Safety Study vs. Placebo**
LIMBREL was evaluated in a 60-day randomized, double-blind, placebo-controlled safety trial. Subjects were sex matched and recruited from ages 40 to 75. Safety was measured by the incidence of treatment emergent adverse events and laboratory abnormalities. When LIMBREL at 250 mg per day was compared with placebo after administration to a healthy human population, no changes in blood chemistry or serology were observed.

**ADVERSE REACTIONS**
In a randomized, double-blind placebo-controlled safety study of 60 days, subjects ingested either 125 mg of LIMBREL or placebo. Rates of symptomatic adverse events were low and did not differ between the LIMBREL and placebo arms. There were also no usage-related changes in routine hematological or biochemical safety parameters.

Adverse reactions were also collected in a double-blind, randomized clinical trial of 30 days, although this study was not designed to specifically assess usage-related differences in adverse events. Overall, no serious adverse events were reported for LIMBREL. There was a non-significant trend toward more frequent edema and nonspecific musculoskeletal events in the naproxen arm. No significant changes were observed within or between arms for weight, systolic blood pressure, or diastolic blood pressure. As expected in a trial of this duration, no fecal occult blood was detected in study subjects, including those taking naproxen.

**Side Effects and Rare Events**
***Gastrointestinal (GI) Effects***
Data from an interim analysis of a preliminary study showed that the number of upper GI adverse events of LIMBREL to be about the same as placebo and less than half that of naproxen. Clinical experience by physicians has shown LIMBREL to be well tolerated in patients with a history of mild ulceration. The most common side effects of LIMBREL are nausea, diarrhea and flatulence, which are usually mild and do not usually require cessation of use of LIMBREL.

### *Hepatic (liver) Effects*
Twelve cases of elevated hepatocellular enzyme tests have been reported to Primus, two in clinical trials and ten in post-marketing surveillance. In all but one case the abnormalities were mild (2-3 times normal) and without symptoms. In one case the abnormality was more severe and associated with clinical jaundice. All resolved without treatment after LIMBREL was stopped.

### *Pulmonary (lung) Effects*
Three cases of hypersensitivity pneumonitis (allergic lung disease) have been reported to Primus. All three cases required treatment and two were hospitalized although all recovered.

### *Renal (kidney) Effects*
No reports of renal toxicity have been received by Primus and Primus has not noted any renal abnormalities in clinical trials to date. Limbrel has been used in people with renal insufficiency as reported by practicing nephrologists and other physicians. In people with renal insufficiency, Primus recommends renal function be followed according to physicians' usual mode of practice.

## Special Studies
### *Gastrointestinal*
In a retrospective study, 8 healthy adult subjects, ranging in age from 41 to 60 years, ingested LIMBREL daily for periods ranging from 5 to 11 months (mean 7 months). Daily amount ranged from 300 mg to 1,500 mg (mean of 825 mg). Six subjects were male and 2 were female. No subjects reported a prior history of gastrointestinal ulceration. Analysis for fecal occult blood was conducted on three consecutive days. No subjects in this trial were positive for fecal occult blood.

In a second retrospective study, 13 healthy adult subjects ranging in age from 38 to 58 ingested LIMBREL daily for periods ranging from 5 to 15 months (mean of 8 months). Daily administration ranged from 150 mg to 600 mg (mean of 375 mg). Seven subjects were male and 6 subjects were female. No subjects reported a prior history of gastrointestinal illness. Analysis for fecal occult blood was conducted on three consecutive days. No subjects in this trial were positive for fecal occult blood. One subject had an event of occult bleeding prior to the measurement date, withdrew from the product, and was unavailable for retrospective analysis. This subject was found to have an unreported prior history of gastrointestinal ulceration. The most commonly reported LIMBREL adverse event in all clinical trials is diarrhea and flatulence occuring in 5-8% of subjects. No subject has discontinued participation in a trial because of these symptoms.

Endoscopic examinations have not been conducted in LIMBREL users.

## Special Populations
### *Patients Anticoagulated with Warfarin*
LIMBREL was administered to 59 patients who were taking warfarin chronically. Prothrombin times measured 2 weeks after the addition of LIMBREL were unchanged in the majority of patients. In 2 patients the prothrombin time was lengthened and in 2 patients was shortened beyond 2 standard deviations. It is not known whether these represented variation in laboratory testing or reflect a CYP450 polymorphism affecting warfarin

metabolism. Because of this, physicians are advised to check prothrombin time one to two weeks after initiating LIMBREL in patients anticoagulated with warfarin.

Clinical studies have not been performed to assess the safety and efficacy of LIMBREL in pediatric, geriatric, hepatic insufficiency, renal insufficiency, and immunologically compromised patient populations.

**Post-Marketing Surveillance**
In post marketing surveillance through June 2008 of over 85,000 patients of LIMBREL, a total of 94 cases (0.1%) of side effects were reported. The most serious side effects were 1 case of bronchiolitis obliterans, 2 cases of hypersensitivity pneumonitis, 1 case of upper gastrointestinal bleeding, and 10 cases of elevation of hepatocellular enzyme tests, all of which resolved without residual effects after discontinuing LIMBREL. Notably, no serious or acute cardiovascular events have been reported. One case of first trimester miscarriage has been reported in a patient taking 7 prescription drugs concomitantly (including 2 drugs with warnings against use during pregnancy). The relevance of this case to LIMBREL is unknown. No other serious events have been reported.

**RECOMMENDED USE**
LIMBREL is intended for the clinical dietary management of the metabolic processes of osteoarthritis (OA).

**DISCLAIMED USE**
LIMBREL has not been investigated for use in the clinical dietary management of rheumatoid arthritis (RA), acute pain or primary dysmenorrhea.

**PRECAUTIONS AND CONTRAINDICATIONS**
**General**
LIMBREL is contraindicated in an extremely small number of patients with hypersensitivity to any component of flavocoxid or to flavonoids. Foods rich in flavonoid contents include: colored fruits and vegetables, dark chocolate, tea (especially green tea), red wine, and Brazil nuts.

**Pediatric, Pregnancy and Lactation**
There are no formal studies with LIMBREL in patients under the age of 18 years of age or pregnant or lactating patients. For this reason, LIMBREL is not recommended for pediatric, pregnant or lactating patients.

**Over Usage**
There are no known cases of LIMBREL over usage. Animal studies have shown that consuming the equivalent of at least 10 times the recommended human usage of 500 to 1,000 mg/day did not produce adverse events. However, as in most over usage situations, symptoms following an over usage of LIMBREL could vary according to the patient. If an over usage were to occur, patients should be managed by systematic and supportive care as soon as possible following product consumption.

**Physician Supervision**
**LIMBREL is a medical food product dispensed by prescription and must be used under physician supervision.**

## PRODUCT ADMINISTRATION

### Recommended Administration

For the clinical dietary management of the metabolic processes of OA, take either one 250 mg or one 500 mg capsule every 12 hours for 500 mg to 1,000 mg total daily consumption, or as directed by a physician. LIMBREL is safe taken with or without other foods. If patients forget to take the prescribed amount, take it as soon as they remember and then resume the normal schedule as directed by a physician.

### How Supplied

LIMBREL is supplied in 250 mg and 500 mg capsules. LIMBREL 250 mg capsules are in two-part turquoise green capsules with a smooth surface imprinted "LIMBREL" on one end and "52001" on the other end, supplied as:

| # | Size |
|---|---|
| 68040-601-16 | Bottle of 60 capsules (250 mg) |
| 68040-601-18 | Carton of 120 capsule (250 mg) packets containing 20 packs of 6-capsule packets each as a sample package (*Not For Resale*) |
| 68040-601-12 | Carton of 20 capsule (250 mg) packets containing 1 capsule each as a sample package (*Not For Resale*) |
| 68040-601-13 | Carton of 20 capsule (250 mg) blister cards containing 2 capsules each as a sample package (*Not For Resale*) |
| 68040-601-02 | Blister Card of 2 capsules (250 mg) as a sample (*Not For Resale*) |
| 68040-601-01 | Packet of 1 capsule (250 mg) as a sample (*Not For Resale*) |

LIMBREL 500 mg capsules are in two-part turquoise green capsules with a smooth surface imprinted with two white stripes on the cap, and imprinted "LIMBREL" and "52002" on the body, supplied as:

| # | Size |
|---|---|
| 68040-602-16 | Bottle of 60 capsules (500 mg) |
| 68040-602-12 | Carton of 20 capsule (500 mg) packets containing 1 capsule each as a sample package (*Not For Resale*) |
| 68040-602-01 | Packet of 1 capsule (500 mg) as a sample (*Not For Resale*) |

Store at room temperature, 59-86°F (15-30°C) [see USP Controlled Room Temperature]. Protect from light and moisture. LIMBREL is supplied to pharmacies in a recyclable plastic bottle with a child-resistant cap. Dispense in a light-resistant container as defined in the USP/NF with a child-resistant closure.

**Dispensed by prescription.**

Manufactured by: Cornerstone Research and Development, Farmington, UT 84025; Avéma Pharma Solutions, Miami, FL 33172; Nutritional Laboratories International, Missoula, MT 59801

Manufactured for: Primus Pharmaceuticals, Inc., Scottsdale, AZ 85251
1-480-483-1410 www.limbrel.com
U.S. Patent No. 7,108,868 and 7,192,611; Other patents pending.

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