Product Information

LIMBREL®
flavocoxid, 250 mg and 500 mg capsules for oral administration.
LIMBREL®250
LIMBREL® 500
flavocoxid and citrated zinc bisglycinate, 250 mg/50 mg, 500 mg/50 mg capsules for oral administration.
Dispensed by prescription.
(U.S. patents 5,516,925; 7,108,868; 7,192,611; and 7,514,469; other patents pending.)

A specially formulated medical food product, consisting primarily of a proprietary blend of flavonoid (polyphenol) ingredients with or without a zinc chelate, for the clinical dietary management of the metabolic processes associated with 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., TNFα, IL-β, 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.

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, respectively. 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 that are strong chemoattractant (LTB_4) and vasoactive (LTC_4, (LTD_4, and LTE_4) molecules responsible for the migration of white blood cells (WBCs) to the site of injury and vasoconstriction of blood vessels, respectively. 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 by NSAIDs 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 by 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.

Some OA patients have nutritional deficiencies of zinc. In addition, zinc chelates manage gastric mucosal damage from NSAIDs and *Helicobacter pylori*. A meta-analysis of 13 trials comprising 757 subjects treated with zinc chelates demonstrate that by endoscopic measurements and ulcer healing rates were equivalent to H2 blockers. A number of studies also show that the incidence of ulceration, while on NSAIDs, is reduced while taking a zinc chelate. This suggests that zinc may be essential to maintaining gastric mucosal integrity in some patients.

DESCRIPTION

Primary Ingredients

LIMBREL (flavocoxid) is classified as a medical food, a regulatory category distinct from drugs and supplements. Limbrel is 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), a regulatory requirement for medical foods. 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.

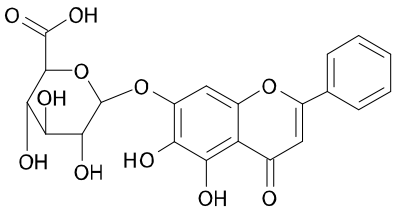
Flavonoids

Flavonoids are a group of phytochemicals 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 osteoarthritis. OA may not be managed simply by a change in the normal diet due to the high volume of vegetable and fruit matter that would need to be consumed.

Baicalin

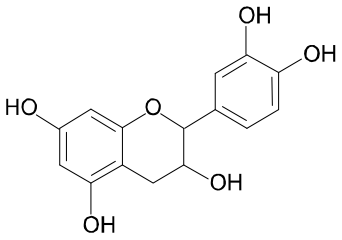
The primary Free-B-Ring flavonoid is baicalin (5,6,7-trihydroxyflavone,7-O-β-D-glucuronopyranoside), derived from the phytochemical food source material *Scutellaria baicalensis*. Its molecular formula is $C_{21}H_{18}O_{11}$, a molecular weight of 446.37 and the following chemical structure:



Baicalin

Catechin

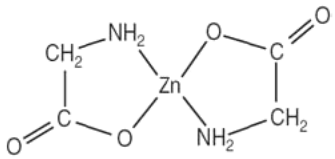
The primary flavans are catechin (3,3',4',5,7-pentahydroxyflavan (2R,3S form)), and its stereo-isomer, epicatechin (3,3',4',5,7-pentahydroxyflavan (2R,3R form)) from the phytochemical food source material *Acacia catechu*. Its molecular formula is $C_{15}H_{14}O_6$, a molecular weight of 290.27 and the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



Catechin

LIMBREL250 and LIMBREL500 Also Contain Citrated Zinc Bisglycinate

Each LIMBREL250 and LIMBREL500 capsules contains 50 mg citrated zinc bisglycinate, a glycine amino acid chelate of zinc formed in the presence of citric acid that provides approximately 10 mg of elemental zinc per capsule. Zinc is an essential mineral co-factor required by many enzymes in the body, including those related to both bone and cartilage metabolism. This zinc bisglycinate has been shown to have improved absorption over inorganic zinc salts, such as zinc sulfate. Zinc bisglycinate is a complex with an empirical formula of $C_4H_8O_4Zn$, and a molecular weight of 215.5. Its structural formula is:



Citrated zinc bisglycinate

Other Ingredients

LIMBREL contains the following "inactive" 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 [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 regulatory definition of a medical food. LIMBREL products are to be used under a physician's supervision and are dispensed by prescription.

[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

All LIMBREL products are yellow to light brown powders that are partially soluble in water and glycerol, soluble in ethanol, methanol, and acetonitrile and are practically insoluble in hexane. Each capsule of LIMBREL contains 250 mg or 500 mg of flavocoxid, as noted in the Primary

Ingredients Section. LIMBREL250 and LIMBREL500 also contain 50 mg of citrated zinc bisglycinate which provides approximately 10 mg of elemental zinc per capsule.

CLINICAL PHARMACOLOGY

Mechanism of Action

The COX enzymes have two sites of metabolism: the cyclooxygenase active site converts AA to prostaglandin G2 (PGG_2), followed by conversion of this intermediate by the peroxidase moiety to PGH_2. PGH_2 is then converted to thromboxane, prostaglandins and prostacyclin by a variety of isomerases and synthases present in cells and platelets. All NSAIDs work by inhibiting the first site of metabolism, cyclooxygenase, in the COX enzymes effectively stopping any further metabolism toward fatty acids which are key mediators of systemic organ function and other physiological processes in the body. *In vitro* enzyme studies have shown that LIMBREL inhibits the peroxidase moieties of COX-1 and COX-2. Because LIMBREL inhibits only the second, sequential site of AA metabolism in the COX enzymes, PGG_2 is still converted to PGH_2 by redundant peroxidase activities in cells and platelets. LIMBREL, compared to a several traditional NSAIDs and selective COX-2 inhibitors, was the only entity shown to inhibit 5-LOX in enzyme assays. Cell and animal studies have shown that inducible prostaglandin and leukotriene production from COX-2 and 5-LOX, respectively, is damped by LIMBREL. This proposed “dual inhibition” of COX and LOX manages the metabolic inflammation from these enzyme pathways with minimal effects on organ function as shown in laboratory studies and well-controlled clinical trials. This relatively balanced down-regulation of these enzymatic pathways is somewhat weaker than 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 a total oxygen radical absorbance capacity ($ORAC_{total}$) of 3719 μmolTE/g, as compared to Vitamin E (1,100 μmolTE/g) and Vitamin C (2,000 μmolTE/g). LIMBREL also has a hydroxyl radical absorbance capacity (HORAC) value of 1326 μmol CAE/g for hydroxyl radicals and a peroxynitrite radical averting capacity (NORAC) of 1936 μmolTE/g, both of which directly destroy cartilage. In cell and animal studies, LIMBREL has been shown to decrease activation of nuclear factor κB (NFκB), a key transcription factor activated by oxidative species which induces cytokines (ie., IL-1β, IL-6, TNFα), COX-2, 5-LOX and inducible nitric oxide synthase (iNOS) in cell and animal studies. LIMBREL also restores IκBα, the cytoplasmic controlling factor of NFκB. As a consequence of a high and varied antioxidant capacity which down-regulates NFκB and up-regulates IκBα, LIMBREL decreases IL-1β, IL-6, TNFα, COX-2, 5-LOX and iNOS expression in cell and animal studies without effecting COX-1. LIMBREL also decreases the levels of malondialdehyde, a direct oxidative product of AA, in cell studies.

Platelet Interactions

In a clinical trial using normal volunteers, LIMBREL administered for 14 days at 500 mg BID, had no effect on platelet aggregation or bleed times compared to baseline values. In an animal study, LIMBREL showed no interaction with aspirin.

Pharmacokinetics

Absorption*:* Peak plasma concentration of baicalein, the gut-bacterial digestion product of baicalin, occurred at 5.8 hours after oral dose. Under fasting conditions, the average AUC was 7,007 μg/mL/hour, Cmax was 0.93 μg/mL, and the $T_{1/2}$ was approximately 11–12 hours. Catechin reached a peak plasma level at about 1.5 hours after oral dose and the $T_{1/2}$ was approximately 3-4 hours.

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. Food does not affect the metabolism of LIMBREL and may reduce occasional mild 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). Baicalin, undergoes hydrolysis of the glucuronide moiety in the upper intestine by 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 significant 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%

Nonclinical Toxicology

Animal Toxicology: 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 daily usage) 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 compared with age and sex matched placebo treated control groups of healthy subjects. Observations across all groups revealed no behavioral abnormalities, differences in weight gain, abnormalities in hepatic, renal, gastric, or duodenal histology or changes in serum electrolytes, liver enzyme levels or markers of renal function.

Zinc Toxicology (elemental): For LIMBREL products containing zinc, each capsule provides approximately 10 mg of elemental zinc. The National Academy of Sciences upper acceptable limit for self-administration is 40 mg/day of elemental zinc, the equivalent of four LIMBREL capsules per day. Zinc is considered acutely toxic at 200 mg elemental zinc per day, the equivalent of 20 LIMBREL capsules per day.

CLINICAL EXPERIENCE

LIMBREL has demonstrated significant functional and symptomatic improvements in clinical trial subjects 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 105 subjects with 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 and subject VAS scales for global response and discomfort. 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.

In this study, both LIMBREL and naproxen arms noted significant reduction in the signs and symptoms of knee OA. All within-group improvements in efficacy endpoints were statistically significant ($p \leq 0.001$). The LIMBREL and naproxen groups 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*

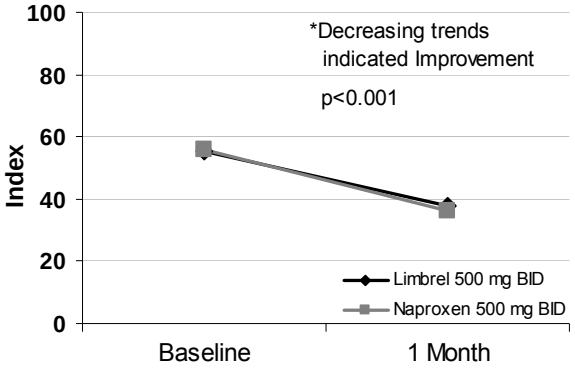


Figure 2. Improvement in Physician VAS (Global Disease Assessment)**

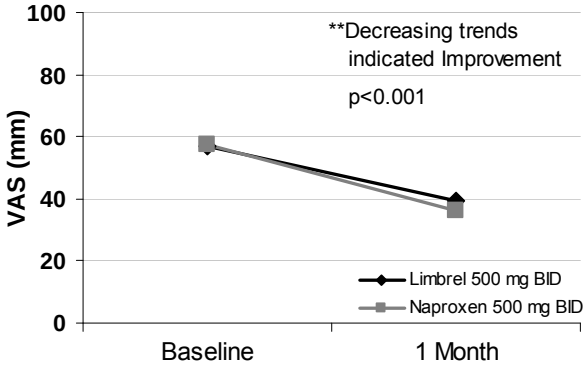


Figure 3. Improvement in Subject VAS (Global Disease Assessment)†

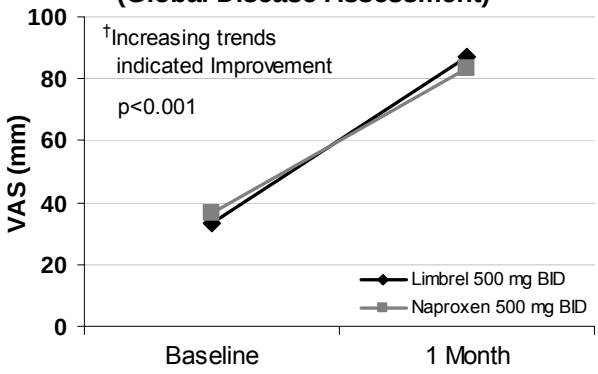
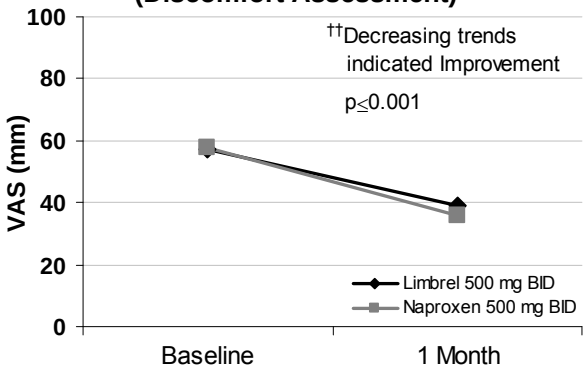


Figure 4. Improvement in Subject VAS (Discomfort Assessment) ††



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.

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 and Efficacy Study vs. Naproxen

In a 3 month randomized, multicenter, double blind study of 220 subjects with moderate-severe OA of the knee, LIMBREL (500 mg twice daily) demonstrated equivalent efficacy and statistically better upper GI and renal safety compared to naproxen (500 mg twice daily) at 6 or 12 weeks. Subjects were sex-matched and recruited from ages 35 to 80 years with an average age of 60 years per group. There were no differences in demographic characteristics or in baseline WOMAC or VAS scores between the two groups. The trial was structured to show non-inferiority of flavocoxid to naproxen. Primary outcome measures included the WOMAC and subscales and a timed walk. Secondary outcome measures included investigator global assessment of disease activity (IGAD), subject global response to therapy (SGRT), subject global assessment of disease activity (SGAD) and subject global assessment of discomfort (SGADc).

In this study, both LIMBREL and naproxen groups noted significant reduction in the signs and symptoms of knee OA. All within-group improvements in efficacy endpoints were statistically significant ($p \leq 0.001$). The LIMBREL and naproxen groups performed nearly identically with an above 90% response rate as measured by WOMAC composite index, and the between group differences were not statistically significant for any efficacy endpoint. See Figures 5-6 below for efficacy results of LIMBREL vs. naproxen in this study.

Figure 5. Improvement in Mean WOMAC Index

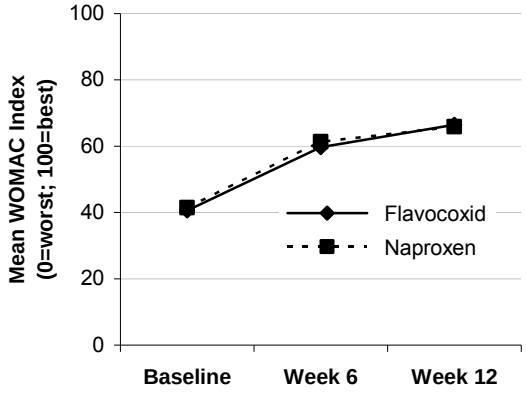
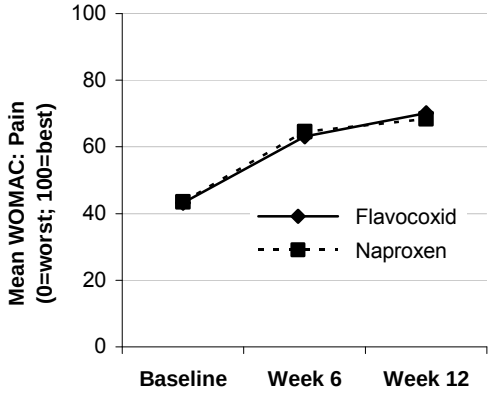


Figure 6. Improvement in Mean WOMAC Pain



Interesting trends were noted and several important statistically significant differences were discovered in the subset analyses by comparing p-values between groups at 6 and 12 weeks (Table 3).

Table 3: Comparison of Selected Measures (p-values)
LIMBREL vs. Naproxen

All subjects; raw number change	p-value, 6 weeks	p-value, 12 weeks
WOMAC composite	0.74	0.26
WOMAC phys function	0.96	0.23
IGAD	0.97	0.62
30 ft timed walk	0.21	0.1
SGRT	0.06	0.59
All subjects; % change		
WOMAC composite	0.74	0.1
WOMAC phys function	0.96	0.09
IGAD	0.97	0.69
30 timed walk	0.25	0.08
SGRT	0.06	0.59

Stratifying the data to midpoint values of the total population to specific measures demonstrated significant improvement of LIMBREL over naproxen. IGAD was most predictive for improvement in efficacy of LIMBREL over naproxen (Table 4).

Table 4: Comparison of Selected Measures in Subset Populations with IGAD <8; LIMBREL vs. Naproxen

With IGAD<8	6 weeks % change Mean±SEM	12 weeks % change Mean±SEM	6 weeks p-value	12 weeks p-value
WOMAC index				
LIMBREL	77.43±16.84	96.37±17.90	<0.0001	<0.0001
Naproxen	58.63±7.96	75.08±9.43		
WOMAC Pain				
LIMBREL	74.6±18.31	94.02±20.44	<0.0001	<0.0001
Naproxen	61.79±7.18	77.36±9.11		
WOMAC Stiffness				
LIMBREL	53.85±10.89	83.01±16.43	0.15	0.08
Naproxen	45.98±6.48	72.17±8.87		
WOMAC Physical Function				
LIMBREL	84.13±19.41	104.64±21.96	0.04	0.03
Naproxen	58.69±8.20	76.13±9.66		
Time Walk (sec)				
LIMBREL	-16.08±1.94	-23.87±2.61	0.01	0.002
Naproxen	-12.03±1.07	-17.51±1.46		
SGRT				
LIMBREL	6.47±0.22	6.98±0.26	0.04	0.003
Naproxen	5.67±0.22	6.07±0.22		
IGRT				
LIMBREL	6.21±0.23	6.84±0.26	0.05	0.01
Naproxen	5.52±0.21	6.02±0.20		

Taken together, these data suggest a delayed response to flavocoxid, consistent with the known pharmacodynamics of flavonoid molecules.

Safety

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 differences in adverse events or routine safety hematology or serum chemistry laboratory values were observed.

In another randomized, double-blind placebo-controlled safety study of 12 weeks, subjects ingested (n=59) either 250 mg of LIMBREL or placebo. Rates of symptomatic adverse events were low and did not differ between the LIMBREL and placebo groups. LIMBREL exhibited statistically fewer upper respiratory adverse events (p=0.0003) compared to placebo. 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 of LIMBREL (500 mg twice daily) vs. naproxen (500 mg twice daily) (n=105) described above. Although this study was not designed specifically to assess usage-related differences in adverse events, no serious adverse events were reported for LIMBREL or naproxen. 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. No fecal occult blood was detected in study subjects from either arm.

In the randomized, double-blind safety and efficacy study of 12 weeks for LIMBREL (500 mg twice daily) vs. naproxen (500 mg twice daily) (n=220) described above, a total of 71 adverse events were recorded in each group (67% flavocoxid, 62% naproxen). Of these, 45 (42.5%) in the flavocoxid group and 51 (44.7%) in the naproxen group were considered by investigators to be related to study product. No serious AEs were noted. Two positive fecal occult bloods were found, one in each study group. These were not associated with any GI symptoms, change in hematocrit or other abnormalities. The following were reported between 1-4% of the population: arthralgia, headache, insomnia, respiratory symptoms (bronchitis, laryngitis, pharyngitis, rhinitis combined), diarrhea, dyspepsia, nausea, edema, abnormal liver function tests, hyperglycemia, hyperuricemia, hypercholesterolemia, and increased BUN. Of these, there were significantly more episodes of edema (p=0.016) and dyspepsia (p=0.041) in the naproxen group and flatulence (p=0.042) in the flavocoxid group. There were trends, without statistical significance, suggesting elevation of BUN, potassium and serum uric acid in the naproxen group and similar trends toward more abnormal liver function tests in the flavocoxid group. There was an increase in total GI complaints, total respiratory complaints, constipation and nausea in the naproxen group and somnolence in the flavocoxid group.

Side Effects and Rare Events

Gastrointestinal (GI) Effects

In post-marketing surveillance, clinical experience by physicians has shown LIMBREL to be well tolerated in patients with a history of mild upper gastrointestinal ulceration. Only one documented upper GI bleed has been reported. The most common side effects of LIMBREL are

nausea, diarrhea and flatulence which are generally mild and do not usually require cessation of use of LIMBREL. No endoscopic clinical studies have been conducted. In an 8 week, phase IV-like open label post-marketing study (n=1067), LIMBREL was better tolerated in patients who had to stop NSAIDs previously due to GI intolerance of other NSAIDs. Of patients on gastroprotective medication, 31% either decreased or ceased their use of these medications over the course of the study.

Hepatic (liver) Effects

Borderline elevations (1.2 to 3 times the upper limit of normal) of one or more liver tests without other signs or symptoms occurred in controlled clinical trials in less than 10% of subjects. Notable elevations of ALT and AST (approximately >3 to 5 times upper limit of normal) occurred in controlled clinical trials in less than 2% of subjects. These laboratory abnormalities may be transient, may remain unchanged, or may progress with continuing therapy. Rare cases of severe hepatic reactions accompanied by jaundice or eosinophilia have been reported. All of these cases resolved within 2-4 weeks without residua after LIMBREL was discontinued. Hepatic abnormalities may be the result of a hypersensitivity reaction to one of the components of LIMBREL. No unifying predisposing factors have been identified. If abnormal liver tests (including bilirubin) persist or worsen, if clinical signs and/or symptoms consistent with liver disease develop, or if systemic manifestations occur (e.g., eosinophilia, rash, abdominal pain, diarrhea, dark urine, etc.), LIMBREL should be discontinued immediately.

Pulmonary (lung) Effects

Rare (<0.003%) cases of hypersensitivity pneumonitis have been reported. These occurred without warning or predictive ability in patients without history of allergy, atopy or prior pulmonary disease. Patients exhibited symptoms of fever, cough, hypoxemia and diffuse pulmonary infiltrates. All patients required supplemental oxygen and parenteral corticosteroids but recovered uneventfully and without residua.

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 Populations

Patients Anticoagulated with Warfarin

LIMBREL was administered to 59 patients who were taking warfarin chronically. Prothrombin times measured before and 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. However, none of these deviations exceeded 2 standard deviations from the mean and did not result in stoppage of therapy. 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.

Other Special Populations
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 March 2011 with over 285,000 patients exposed to LIMBREL, a total of 208 cases (0.1%) of side effects were reported. The most serious side effects were 10 cases of hypersensitivity pneumonitis, 2 cases of upper gastrointestinal bleeding (only 1 documented), and 21 cases of elevation of hepatocellular enzyme tests, including 4 cases of jaundice, all of which resolved without residual effects after discontinuing LIMBREL. No serious or acute cardiovascular events have been reported. One case of first trimester miscarriage has been reported in a patient taking multiple prescription drugs concomitantly. 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).

PRECAUTIONS AND CONTRAINDICATIONS
General
LIMBREL is contraindicated in patients with hypersensitivity to any component of flavocoxid or to flavonoids. Foods rich in flavonoid 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 these population groups.

Over Usage
There are no known cases of LIMBREL over usage with the non-zinc formulation (see precautions for zinc under zinc toxicology section). Animal studies using the non-zinc containing product 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 induction of vomiting 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
For the clinical dietary management of the metabolic processes of OA, take either one 250 mg or one 500 mg capsule with or without zinc 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, they should 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)
68040-601-12	Carton of 20 capsule (250 mg) packets containing 1 capsule each as a sample package (*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*)

LIMBREL250 capsules with 50 mg citrated zinc bisglycinate (10 mg elemental zinc) are in two-part turquoise green capsules with a smooth surface imprinted “LIMBREL” on one end and “52005” on the other end, supplied as:

#.	Size
68040-605-16	Bottle of 60 capsules (250/50 mg)
68040-605-12	Carton of 20 capsule (250/50 mg) packets containing 1 capsule each as a sample package (Not For Resale)
68040-605-01	Packet of 1 capsule (250/50 mg) as a sample (*Not For Resale*)

LIMBREL500 capsules with 50 mg citrated zinc bisglycinate (10 mg elemental zinc) are in two-part turquoise green capsules with a smooth surface imprinted with two white stripes on the cap, and imprinted “LIMBREL” and “52006” on the body, supplied as:

#.	Size
68040-606-16	Bottle of 60 capsules (500/50 mg)
68040-606-08	Carton of 10 capsules (500/50 mg) in a blister sample pack (*Not For Resale*)

Store at room temperature, 59-86^{o}F (15-30^{o}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, Ogden, UT 84404; Nutritional Laboratories International, Missoula, MT 59801

Manufactured for: Primus Pharmaceuticals, Inc., Scottsdale, AZ 85251
1-480-483-1410 www.limbrel.com

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