RL:LX
PRESCRIBING INFORMATION

RELAFEN®
(nabumetone)
Tablets

Cardiovascular Risk

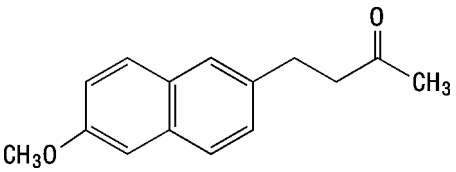
- NSAIDs may cause an increased risk of serious cardiovascular thrombotic events, myocardial infarction, and stroke, which can be fatal. This risk may increase with duration of use. Patients with cardiovascular disease or risk factors for cardiovascular disease may be at a greater risk (See WARNINGS).
- RELAFEN is contraindicated for the treatment of peri-operative pain in the setting of coronary artery bypass graft (CABG) surgery (see WARNINGS).

Gastrointestinal Risk

- NSAIDs cause an increased risk of serious gastrointestinal adverse events including bleeding, ulceration, and perforation of the stomach or intestines, which can be fatal. These events can occur at any time during use and without warning symptoms. Elderly patients are at greater risk for serious gastrointestinal events (see WARNINGS).

DESCRIPTION

RELAFEN (nabumetone) is a naphthylalkanone designated chemically as 4-(6-methoxy-2-naphthalenyl)-2-butanone. It has the following structure:



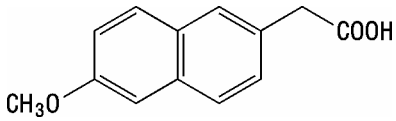
Nabumetone is a white to off-white crystalline substance with a molecular weight of 228.3. It is nonacidic and practically insoluble in water, but soluble in alcohol and most organic solvents. It has an n-octanol:phosphate buffer partition coefficient of 2400 at pH 7.4.

Tablets for Oral Administration: Each oval-shaped, film-coated tablet contains 500 mg or 750 mg of nabumetone. Inactive ingredients consist of hypromellose, microcrystalline cellulose, polyethylene glycol, polysorbate 80, sodium lauryl sulfate, sodium starch glycolate, and titanium dioxide. The 750-mg tablets also contain iron oxides.

CLINICAL PHARMACOLOGY

RELAFEN is a non-steroidal anti-inflammatory drug (NSAID) that exhibits anti-inflammatory, analgesic, and antipyretic properties in pharmacologic studies. As with other non-steroidal anti-inflammatory agents, its mode of action is not known; however, the ability to inhibit prostaglandin synthesis may be involved in the anti-inflammatory effect.

The parent compound is a prodrug, which undergoes hepatic biotransformation to the active component, 6-methoxy-2-naphthylacetic acid (6MNA), that is a potent inhibitor of prostaglandin synthesis.



It is acidic and has an n-octanol:phosphate buffer partition coefficient of 0.5 at pH 7.4.

Pharmacokinetics: After oral administration, approximately 80% of a radiolabelled dose of nabumetone is found in the urine, indicating that nabumetone is well absorbed from the gastrointestinal tract. Nabumetone itself is not detected in the plasma because, after absorption, it undergoes rapid biotransformation to the principal active metabolite, 6-methoxy-2-naphthylacetic acid (6MNA). Approximately 35% of a 1,000-mg oral dose of nabumetone is converted to 6MNA and 50% is converted into unidentified metabolites which are subsequently excreted in the urine. Following oral administration of RELAFEN, 6MNA exhibits pharmacokinetic characteristics that generally follow a one-compartment model with first order input and first order elimination.

6MNA is more than 99% bound to plasma proteins. The free fraction is dependent on total concentration of 6MNA and is proportional to dose over the range of 1,000 mg to 2,000 mg. It is 0.2% to 0.3% at concentrations typically achieved following administration of 1,000 mg of RELAFEN and is approximately 0.6% to 0.8% of the total concentrations at steady state following daily administration of 2,000 mg.

Steady-state plasma concentrations of 6MNA are slightly lower than predicted from single-dose data. This may result from the higher fraction of unbound 6MNA which undergoes greater hepatic clearance.

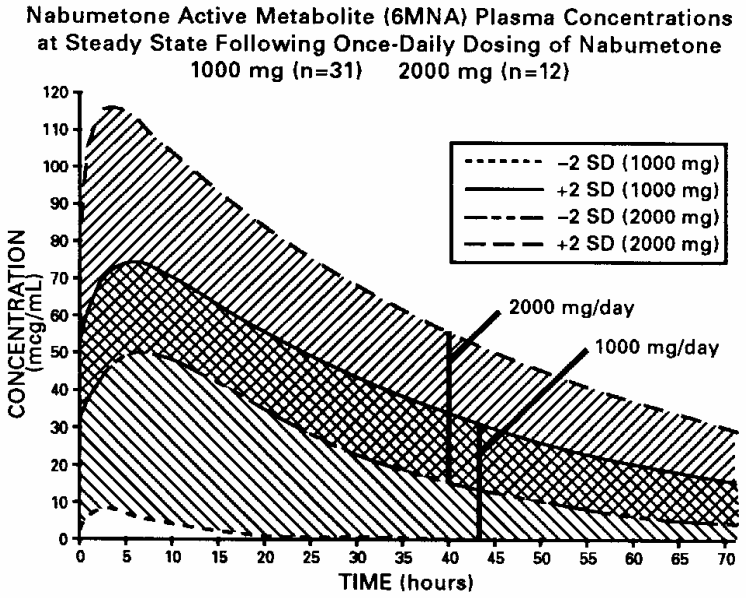
Coadministration of food increases the rate of absorption and subsequent appearance of 6MNA in the plasma but does not affect the extent of conversion of nabumetone into 6MNA. Peak plasma concentrations of 6MNA are increased by approximately one third.

Coadministration with an aluminum-containing antacid had no significant effect on the bioavailability of 6MNA.

Table 1. Mean Pharmacokinetic Parameters of Nabumetone Active Metabolite (6MNA) at Steady State Following Oral Administration of 1,000-mg or 2,000-mg Doses of RELAFEN

Abbreviation (units)	Young Adults Mean ± SD 1,000 mg n = 31	Young Adults Mean ± SD 2,000 mg n = 12	Elderly Mean ± SD 1,000 mg n = 27
T_{max} (hr)	3.0 (1.0 to 12.0)	2.5 (1.0 to 8.0)	4.0 (1.0 to 10.0)
$t_{½}$ (hr)	22.5 ± 3.7	26.2 ± 3.7	29.8 ± 8.1
CL_{ss}/F (mL/min)	26.1 ± 17.3	21.0 ± 4.0	18.6 ± 13.4
Vd_{ss}/F (L)	55.4 ± 26.4	53.4 ± 11.3	50.2 ± 25.3

The simulated curves in the graph below illustrate the range of active metabolite plasma concentrations that would be expected from 95% of patients following 1,000-mg to 2,000-mg doses to steady state. The cross-hatched area represents the expected overlap in plasma concentrations due to intersubject variation following oral administration of 1,000 mg to 2,000 mg of RELAFEN.



6MNA undergoes biotransformation in the liver, producing inactive metabolites that are eliminated as both free metabolites and conjugates. None of the known metabolites of 6MNA has been detected in plasma. Preliminary in vivo and in vitro studies suggest that unlike other NSAIDs, there is no evidence of enterohepatic recirculation of the active metabolite. Approximately 75% of a radiolabelled dose was recovered in urine in 48 hours. Approximately 80% was recovered in 168 hours. A further 9% appeared in the feces. In the first 48 hours, metabolites consisted of:

–nabumetone, unchanged	not detectable
–6-methoxy-2-naphthylacetic acid (6MNA), unchanged	<1%
–6MNA, conjugated	11%
–6-hydroxy-2-naphthylacetic acid (6HNA), unchanged	5%
–6HNA, conjugated	7%
–4-(6-hydroxy-2-naphthyl)-butan-2-ol, Conjugated	9%
–*O*-desmethyl-nabumetone, conjugated	7%
–unidentified minor metabolites	34%
Total % Dose:	73%

Following oral administration of dosages of 1,000 mg to 2,000 mg to steady state, the mean plasma clearance of 6MNA is 20 to 30 mL/min and the elimination half-life is approximately 24 hours.

Elderly Patients: Steady-state plasma concentrations in elderly patients were generally higher than in young healthy subjects (see Table 1 for summary of pharmacokinetic parameters).

Renal Insufficiency: In moderate renal insufficiency patients (creatinine clearance 30 to 49 mL/min), the terminal half-life of 6MNA was increased by approximately 50% (39.2 ± 7.8 hrs, N=12) compared to the normal subjects (26.9 ± 3.3 hrs, N=13), and there was a 50% increase in the plasma levels of unbound 6MNA.

Additionally, the renal excretion of 6MNA in the moderate renal impaired patients decreased on average by 33% compared to that in the normal patients. A similar increase in the mean terminal half-life of 6MNA was seen in a small study of patients with severe renal dysfunction (creatine

clearance <30 mL/min). In patients undergoing hemodialysis, steady-state plasma concentrations of the active metabolite 6MNA were similar to those observed in healthy subjects. Due to extensive protein binding, 6MNA is not dialyzable.

Dosage adjustment of RELAFEN generally is not necessary in patients with mild renal insufficiency (≥50 mL/min). Caution should be used in prescribing RELAFEN to patients with moderate or severe renal insufficiency. The maximum starting doses of RELAFEN in patients with moderate or severe renal insufficiency should not exceed 750 mg or 500 mg, respectively once daily. Following careful monitoring of renal function in patients with moderate or severe renal insufficiency, daily doses may be increased to a maximum of 1,500 mg and 1,000 mg, respectively (see **WARNINGS, Renal Effects**).

Hepatic Impairment: Data in patients with severe hepatic impairment are limited. Biotransformation of nabumetone to 6MNA and the further metabolism of 6MNA to inactive metabolites is dependent on hepatic function and could be reduced in patients with severe hepatic impairment (history of or biopsy-proven cirrhosis).

Special Studies: ***Gastrointestinal:*** RELAFEN was compared to aspirin in inducing gastrointestinal blood loss. Food intake was not monitored. Studies utilizing ^{51}Cr-tagged red blood cells in healthy males showed no difference in fecal blood loss after 3 or 4 weeks' administration of 1,000 mg or 2,000 mg of RELAFEN daily when compared to either placebo-treated or nontreated subjects. In contrast, aspirin 3,600 mg daily produced an increase in fecal blood loss when compared to subjects who received RELAFEN, placebo, or no treatment. The clinical relevance of the data is unknown.

The following endoscopy trials entered patients who had been previously treated with NSAIDs. These patients had varying baseline scores and different courses of treatment. The trials were not designed to correlate symptoms and endoscopy scores. The clinical relevance of these endoscopy trials, i.e., either G.I. symptoms or serious G.I. events, is not known.

Ten endoscopy studies were conducted in 488 patients who had baseline and post-treatment endoscopy. In 5 clinical trials that compared a total of 194 patients on 1,000 mg of RELAFEN daily or naproxen 250 mg or 500 mg twice daily for 3 to 12 weeks, treatment with RELAFEN resulted in fewer patients with endoscopically detected lesions (>3 mm). In 2 trials a total of 101 patients administered 1,000 mg or 2,000 mg of RELAFEN daily or piroxicam 10 mg to 20 mg for 7 to 10 days, there were fewer patients treated with RELAFEN with endoscopically detected lesions. In 3 trials of a total of 47 patients on 1,000 mg of RELAFEN daily or indomethacin 100 mg to 150 mg daily for 3 to 4 weeks, the endoscopy scores were higher with indomethacin. Another 12-week trial in a total of 171 patients compared the results of treatment with 1,000 mg of RELAFEN daily to ibuprofen 2,400 mg/day and ibuprofen 2,400 mg/day plus misoprostol 800 mcg/day. The results showed that patients treated with RELAFEN had a lower number of endoscopically detected lesions (>5 mm) than patients treated with ibuprofen alone but comparable to the combination of ibuprofen plus misoprostol. The results did not correlate with abdominal pain.

Other: In 1-week, repeat-dose studies in healthy volunteers, 1,000 mg of RELAFEN daily had little effect on collagen-induced platelet aggregation and no effect on bleeding time. In comparison, naproxen 500 mg daily suppressed collagen-induced platelet aggregation and significantly increased bleeding time.

CLINICAL TRIALS

Osteoarthritis: The use of RELAFEN in relieving the signs and symptoms of osteoarthritis (OA) was assessed in double-blind, controlled trials in which 1,047 patients were treated for 6 weeks to

6 months. In these trials, RELAFEN in a dose of 1,000 mg/day administered at night was comparable to naproxen 500 mg/day and to aspirin 3,600 mg/day.

Rheumatoid Arthritis: The use of RELAFEN in relieving the signs and symptoms of rheumatoid arthritis (RA) was assessed in double-blind, randomized, controlled trials in which 770 patients were treated for 3 weeks to 6 months. RELAFEN, in a dose of 1,000 mg/day administered at night, was comparable to naproxen 500 mg/day and to aspirin 3,600 mg/day.

In controlled clinical trials of rheumatoid arthritis patients, RELAFEN has been used in combination with gold, d-penicillamine, and corticosteroids.

~~Individualization of **Dosing**~~

Patient Exposure in Clinical Trials of Osteoarthritis and Rheumatoid Arthritis:

In clinical trials with osteoarthritis and rheumatoid arthritis patients, most patients responded to RELAFEN in doses of 1,000 mg/day administered nightly; total daily dosages up to 2,000 mg were used. In open-labelled studies, 1,490 patients were permitted dosage increases and were followed for approximately 1 year (mode). Twenty percent of patients (n = 294) were withdrawn for lack of effectiveness during the first year of these open-labelled studies. The following table provides patient-exposure to doses used in the US clinical trials:

Table 2. Clinical Double-Blinded and Open-Labelled Trials of RELAFEN in Osteoarthritis and Rheumatoid Arthritis

Dose of RELAFEN	Number of Patients		Mean/Mode Duration of Treatment (yr)	
	OA	RA	OA	RA
500 mg	17	6	0.4/–	0.2/–
1,000 mg	917	701	1.2/1	1.4/1
1,500 mg	645	224	2.3/1	1.7/1
2,000 mg	15	100	0.6/1	1.3/1

As with other NSAIDs, the lowest dose should be sought for each patient. Patients weighing under 50 kg may be less likely to require dosages beyond 1,000 mg; therefore, after observing the response to initial therapy, the dose should be adjusted to meet individual patients' requirements.

INDICATIONS AND USAGE

Carefully consider the potential benefits and risks of RELAFEN and other treatment options before deciding to use RELAFEN. Use the lowest effective dose for the shortest duration consistent with individual patient treatment goals (see WARNINGS).

RELAFEN is indicated for relief of signs and symptoms of osteoarthritis and rheumatoid arthritis.

CONTRAINDICATIONS

RELAFEN is contraindicated in patients with known hypersensitivity to nabumetone or its excipients.

RELAFEN should not be given to patients who have experienced asthma, urticaria, or allergic-type reactions after taking aspirin or other NSAIDs. Severe, rarely fatal, anaphylactic-like reactions to NSAIDs have been reported in such patients (see **WARNINGS, Anaphylactoid Reactions**, and **PRECAUTIONS, General, *Preexisting Asthma***).

RELAFEN is contraindicated for the treatment of peri-operative pain in the setting of coronary artery bypass graft (CABG) surgery (see **WARNINGS**).

WARNINGS

CARDIOVASCULAR EFFECTS

Cardiovascular Thrombotic Events: Clinical trials of several COX-2 selective and nonselective NSAIDs of up to 3 years duration have shown an increased risk of serious cardiovascular (CV) thrombotic events, myocardial infarction, and stroke, which can be fatal. All NSAIDs, both COX-2 selective and nonselective, may have a similar risk. Patients with known CV disease or risk factors for CV disease may be at greater risk. To minimize the potential risk for an adverse CV event in patients treated with an NSAID, the lowest effective dose should be used for the shortest duration possible. Physicians and patients should remain alert for the development of such events, even in the absence of previous CV symptoms. Patients should be informed about the signs and/or symptoms of serious CV events and the steps to take if they occur.

There is no consistent evidence that concurrent use of aspirin mitigates the increased risk of serious CV thrombotic events associated with NSAID use. The concurrent use of aspirin and an NSAID does increase the risk of serious GI events (see **WARNINGS, Gastrointestinal Effects-Risk of Ulceration, Bleeding, and Perforation**).

Two large, controlled, clinical trials of a COX-2 selective NSAID for the treatment of pain in the first 10-14 days following CABG surgery found an increased incidence of myocardial infarction and stroke (see **CONTRAINDICATIONS**).

Hypertension: NSAIDs, including RELAFEN, can lead to onset of new hypertension or worsening of preexisting hypertension, either of which may contribute to the increased incidence of CV events. Patients taking thiazides or loop diuretics may have impaired response to these therapies when taking NSAIDs. NSAIDs, including RELAFEN, should be used with caution in patients with hypertension. Blood pressure (BP) should be monitored closely during the initiation of NSAID treatment and throughout the course of therapy.

Congestive Heart Failure and Edema: Fluid retention and edema have been observed in some patients taking NSAIDs. RELAFEN should be used with caution in patients with fluid retention or heart failure.

Gastrointestinal Effects—Risk of Ulceration, Bleeding, and Perforation: NSAIDs, including RELAFEN, can cause serious gastrointestinal (GI) adverse events including inflammation, bleeding, ulceration, and perforation of the stomach, small intestine, or large intestine, which can be fatal. These serious adverse events can occur at any time, with or without warning symptoms, in patients treated with NSAIDs. Only 1 in 5 patients, who develop a serious upper GI adverse event on NSAID therapy, is symptomatic. Upper GI ulcers, gross bleeding, or perforation caused by NSAIDs occur in approximately 1% of patients treated for 3-6 months, and in about 2-4% of patients treated for 1 year. These trends continue with longer duration of use, increasing the likelihood of developing a serious GI event at some time during the course of therapy. However, even short-term therapy is not without risk.

In controlled clinical trials involving 1,677 patients treated with RELAFEN (1,140 followed for 1 year and 927 for 2 years), the cumulative incidence of peptic ulcers was 0.3% (95% CI; 0%, 0.6%) at 3 to 6 months, 0.5% (95% CI; 0.1%, 0.9%) at 1 year and 0.8% (95% CI; 0.3%, 1.3%) at 2 years. In patients with active peptic ulcer, physicians must weigh the benefits of therapy with RELAFEN

against possible hazards, institute an appropriate ulcer treatment regimen and monitor the patients' progress carefully.

NSAIDs should be prescribed with extreme caution in those with a prior history of ulcer disease or gastrointestinal bleeding. Patients with a *prior history of peptic ulcer disease and/or gastrointestinal bleeding* who use NSAIDs have a greater than 10-fold increased risk for developing a GI bleed compared to patients with neither of these risk factors. Other factors that increase the risk for GI bleeding in patients treated with NSAIDs include concomitant use of oral corticosteroids or anticoagulants, longer duration of NSAID therapy, smoking, use of alcohol, older age, and poor general health status. Most spontaneous reports of fatal GI events are in elderly or debilitated patients and therefore, special care should be taken in treating this population.

To minimize the potential risk for an adverse GI event in patients treated with an NSAID, the lowest effective dose should be used for the shortest possible duration. Patients and physicians should remain alert for signs and symptoms of GI ulceration and bleeding during NSAID therapy and promptly initiate additional evaluation and treatment if a serious GI adverse event is suspected. This should include discontinuation of the NSAID until a serious GI adverse event is ruled out. For high risk patients, alternate therapies that do not involve NSAIDs should be considered.

Renal Effects: Long-term administration of NSAIDs has resulted in renal papillary necrosis and other renal injury. Renal toxicity has also been seen in patients in whom renal prostaglandins have a compensatory role in the maintenance of renal perfusion. In these patients, administration of an NSAID results in a dose-dependent decrease in prostaglandin synthesis and, secondarily, in a reduction of renal blood flow, which may precipitate overt renal decompensation. Patients at greatest risk of this reaction are those with impaired renal function, heart failure, liver dysfunction, those taking diuretics, and the elderly. Discontinuation of NSAID therapy is typically followed by recovery to the pretreatment state.

Advanced Renal Disease: No information is available from controlled clinical studies regarding the use of RELAFEN in patients with advanced renal disease. Therefore, treatment with RELAFEN is not recommended in these patients with advanced renal disease. If RELAFEN therapy must be initiated, close monitoring of the patient's renal function is advisable.

Because nabumetone undergoes extensive hepatic metabolism, no adjustment of the dosage of RELAFEN is generally necessary in patients with mild renal insufficiency; however, as with all NSAIDs, patients with impaired renal function should be monitored more closely than patients with normal renal function (see **CLINICAL PHARMACOLOGY, Pharmacokinetics, *Renal Insufficiency***). In subjects with moderate renal impairment (creatinine clearance 30 to 49 mL/min) there is a 50% increase in unbound plasma 6MNA and dose adjustment may be warranted. The oxidized and conjugated metabolites of 6MNA are eliminated primarily by the kidneys. ~~The extent to which these largely inactive metabolites may accumulate in patients with renal failure has not been studied. As with other drugs whose metabolites are excreted by the kidneys, the possibility that adverse reactions (not listed in ADVERSE REACTIONS) may be attributable to these metabolites should be considered (see CLINICAL PHARMACOLOGY, Pharmacokinetics, *Renal Insufficiency*).~~

Anaphylactoid Reactions: As with other NSAIDs, anaphylactoid reactions may occur in patients without known prior exposure to RELAFEN. RELAFEN should not be given to patients with the aspirin triad. This symptom complex typically occurs in asthmatic patients who experience rhinitis with or without nasal polyps, or who exhibit severe, potentially fatal bronchospasm after taking aspirin or other NSAIDs (see **CONTRAINDICATIONS and PRECAUTIONS, General, *Preexisting Asthma***). Emergency help should be sought in cases where an anaphylactoid reaction occurs.

Skin Reactions: NSAIDs, including RELAFEN, can cause serious skin adverse events such as exfoliative dermatitis, Stevens-Johnson Syndrome (SJS), and toxic epidermal necrolysis (TEN), which can be fatal. These serious events may occur without warning. Patients should be informed about the signs and symptoms of serious skin manifestations and use of the drug should be discontinued at the first appearance of skin rash or any other sign of hypersensitivity.

Pregnancy: In late pregnancy, as with other NSAIDs, RELAFEN should be avoided because it may cause premature closure of the ductus arteriosus.

PRECAUTIONS

General: RELAFEN cannot be expected to substitute for corticosteroids or to treat corticosteroid insufficiency. Abrupt discontinuation of corticosteroids may lead to disease exacerbation. Patients on prolonged corticosteroid therapy should have their therapy tapered slowly if a decision is made to discontinue corticosteroids.

The pharmacological activity of RELAFEN in reducing fever and inflammation may diminish the utility of these diagnostic signs in detecting complications of presumed noninfectious, painful conditions.

Hepatic Effects: Borderline elevations of 1 or more liver function tests may occur in up to 15% of patients taking NSAIDs including RELAFEN. These laboratory abnormalities may progress, may remain unchanged, or may be transient with continuing therapy. Notable elevations of ALT or AST (approximately 3 or more times the upper limit of normal) have been reported in approximately 1% of patients in clinical trials with NSAIDs. In addition, rare cases of severe hepatic reactions, including jaundice and fatal fulminant hepatitis, liver necrosis and hepatic failure, some of them with fatal outcomes have been reported. A patient with symptoms and/or signs suggesting liver dysfunction, or in whom an abnormal liver test has occurred, should be evaluated for evidence of the development of a more severe hepatic reaction while on therapy with RELAFEN. If clinical signs and symptoms consistent with liver disease develop, or if systemic manifestations occur (e.g., eosinophilia, rash, etc.), RELAFEN should be discontinued.

***Hematological Effects*:** Anemia is sometimes seen in patients receiving NSAIDS, including RELAFEN. This may be due to fluid retention, occult or gross GI blood loss, or an incompletely described effect upon erythropoiesis. Patients on long-term treatment with NSAIDs, including RELAFEN, should have their hemoglobin or hematocrit checked if they exhibit any signs or symptoms of anemia.

NSAIDs inhibit platelet aggregation and have been shown to prolong bleeding time in some patients. Unlike aspirin, their effect on platelet function is quantitatively less, of shorter duration, and reversible. Patients receiving RELAFEN who may be adversely affected by alterations in platelet function, such as those with coagulation disorders or patients receiving anticoagulants, should be carefully monitored (see **CLINICAL PHARMACOLOGY, Special Studies, *Oth*er**).

Preexisting Asthma: Patients with asthma may have aspirin-sensitive asthma. The use of aspirin in patients with aspirin-sensitive asthma has been associated with severe bronchospasm which can be fatal. Since cross reactivity, including bronchospasm, between aspirin and other non-steroidal anti-inflammatory drugs has been reported in such aspirin-sensitive patients, RELAFEN should not be administered to patients with this form of aspirin sensitivity and should be used with caution in patients with preexisting asthma.

Photosensitivity: Based on ultraviolet (U.V.) light photosensitivity testing, RELAFEN may be associated with more reactions to sun exposure than might be expected based on skin tanning types.

Information for Patients: Patients should be informed of the following information before initiating therapy with an NSAID and periodically during the course of ongoing therapy. Patients should also be encouraged to read the NSAID Medication Guide that accompanies each prescription dispensed.

1. RELAFEN, like other NSAIDs, may cause serious CV side effects, such as MI or stroke, which may result in hospitalization and even death. Although serious CV events can occur without warning symptoms, patients should be alert for the signs and symptoms of chest pain, shortness of breath, weakness, slurring of speech, and should ask for medical advice when observing any indicative signs or symptoms. Patients should be apprised of the importance of this follow-up (see **WARNINGS, CARDIOVASCULAR EFFECTS**).
2. RELAFEN, like other NSAIDs, can cause GI discomfort and, rarely, serious GI side effects, such as ulcers and bleeding, which may result in hospitalization and even death. Although serious GI tract ulcerations and bleeding can occur without warning symptoms, patients should be alert for the signs and symptoms of ulcerations and bleeding, and should ask for medical advice when observing any indicative sign or symptoms including epigastric pain, dyspepsia, melena, and hematemesis. Patients should be apprised of the importance of this follow-up (see **WARNINGS, Gastrointestinal Effects—Risk of Ulceration, Bleeding, and Perforation**).
3. RELAFEN, like other NSAIDs, can cause serious skin side effects such as exfoliative dermatitis, SJS, and TEN, which may result in hospitalizations and even death. Although serious skin reactions may occur without warning, patients should be alert for the signs and symptoms of skin rash and blisters, fever, or other signs of hypersensitivity such as itching, and should ask for medical advice when observing any indicative signs or symptoms. Patients should be advised to stop the drug immediately if they develop any type of rash and contact their physicians as soon as possible
4. Patients should promptly report signs or symptoms of unexplained weight gain or edema to their physicians.
5. Patients should be informed of the warning signs and symptoms of hepatotoxicity (e.g., nausea, fatigue, lethargy, pruritus, jaundice, right upper quadrant tenderness, and "flu-like" symptoms). If these occur, patients should be instructed to stop therapy and seek immediate medical therapy.
6. Patients should be informed of the signs of an anaphylactoid reaction (e.g. difficulty breathing, swelling of the face or throat). If these occur, patients should be instructed to seek immediate emergency help (see **WARNINGS**).
7. In late pregnancy, as with other NSAIDs, RELAFEN should be avoided because it may cause premature closure of the ductus arteriosus.

Laboratory Tests: Because serious G.I. tract ulceration and bleeding can occur without warning symptoms, physicians should monitor for signs and symptoms of GI bleeding. Patients on long-term treatment with NSAIDs, should have their CBC and a chemistry profile checked periodically. If clinical signs and symptoms consistent with liver or renal disease develop, systemic manifestations occur (e.g., eosinophilia, rash, etc.) or if abnormal liver tests persist or worsen, RELAFEN should be discontinued.

Drug Interactions: ***ACE-inhibitors:*** Reports suggest that NSAIDs may diminish the antihypertensive effect of ACE-inhibitors. This interaction should be given consideration in patients taking NSAIDs concomitantly with ACE-inhibitors.

Aspirin: When RELAFEN is administered with aspirin, its protein binding is reduced, although the clearance of free RELAFEN is not altered. The clinical significance of this interaction is

not known; however, as with other NSAIDs, concomitant administration of nabumetone and aspirin is not generally recommended because of the potential of increased adverse effects.

Diuretics: Clinical studies, as well as post marketing observations, have shown that RELAFEN can reduce the natriuretic effect of furosemide and thiazides in some patients. This response has been attributed to inhibition of renal prostaglandin synthesis. During concomitant therapy with NSAIDs, the patient should be observed closely for signs of renal failure (see **PRECAUTIONS, Renal Effects**), as well as to assure diuretic efficacy.

Lithium: NSAIDs have produced an elevation of plasma lithium levels and a reduction in renal lithium clearance. The mean minimum lithium concentration increased 15% and the renal clearance was decreased by approximately 20%. These effects have been attributed to inhibition of renal prostaglandin synthesis by the NSAID. Thus, when NSAIDs and lithium are administered concurrently, subjects should be observed carefully for signs of lithium toxicity.

Methotrexate: NSAIDs have been reported to competitively inhibit methotrexate accumulation in rabbit kidney slices. This may indicate that they could enhance the toxicity of methotrexate. Caution should be used when NSAIDs are administered concomitantly with methotrexate.

Warfarin: The effects of warfarin and NSAIDs on GI bleeding are synergistic, such that users of both drugs together have a risk of serious GI bleeding higher than users of either drug alone.

In vitro studies have shown that, because of its affinity for protein, 6MNA may displace other protein-bound drugs from their binding site. Caution should be exercised when administering RELAFEN with warfarin since interactions have been seen with other NSAIDs.

Concomitant administration of an aluminum-containing antacid had no significant effect on the bioavailability of 6MNA. When administered with food or milk, there is more rapid absorption; however, the total amount of 6MNA in the plasma is unchanged (see **CLINICAL PHARMACOLOGY, Pharmacokinetics**).

Carcinogenesis, Mutagenesis: In 2-year studies conducted in mice and rats, nabumetone had no statistically significant tumorigenic effect. Nabumetone did not show mutagenic potential in the Ames test and mouse micronucleus test in vivo; however, nabumetone- and 6MNA-treated lymphocytes in culture showed chromosomal aberrations at 80 mcg/mL and higher concentrations (equal to the average human exposure to RELAFEN at the maximum recommended dose).

Impairment of Fertility: Nabumetone did not impair fertility of male or female rats treated orally at doses of 320 mg/kg/day (1,888 mg/m^2) before mating.

Pregnancy: ***Teratogenic Effects: Pregnancy Category C.*** Reproductive studies conducted in rats and rabbits have not demonstrated evidence of developmental abnormalities. However, animal reproduction studies are not always predictive of human response. There are no adequate, well-controlled studies in pregnant women. RELAFEN should be used in pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nonteratogenic Effects: Because of the known effects of non-steroidal anti-inflammatory drugs on the fetal cardiovascular system (closure of ductus arteriosus), use during pregnancy (particularly late pregnancy) should be avoided.

Labor and Delivery: In rat studies with NSAIDs, as with other drugs known to inhibit prostaglandin synthesis, an increased incidence of dystocia, delayed parturition, and decreased pup survival occurred. The effects of RELAFEN on labor and delivery in pregnant women are unknown.

Nursing Mothers: It is not known whether this drug is excreted in human milk, however 6MNA is excreted in the milk of lactating rats. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from RELAFEN, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use: Safety and effectiveness in pediatric patients have not been established.
Geriatric Use: As with any NSAIDs, caution should be exercised in treating the elderly (65 years and older). Of the 1,677 patients in US clinical studies who were treated with RELAFEN, 411 patients (24%) were 65 years or older; 22 patients (1%) were 75 years or older. No overall differences in efficacy or safety were observed between these older patients and younger ones. Similar results were observed in a 1-year, non-US postmarketing surveillance study of 10,800 patients treated with RELAFEN, of whom 4,577 patients (42%) were 65 years or older.

ADVERSE REACTIONS

Adverse reaction information was derived from blinded-controlled and open-labelled clinical trials and from worldwide marketing experience. In the description below, rates of the more common events (greater than 1%) and many of the less common events (less than 1%) represent results of US clinical studies.

Of the 1,677 patients who received RELAFEN during US clinical trials, 1,524 were treated for at least 1 month, 1,327 for at least 3 months, 929 for at least a year, and 750 for at least 2 years. More than 300 patients have been treated for 5 years or longer.

The most frequently reported adverse reactions were related to the gastrointestinal tract and included diarrhea, dyspepsia, and abdominal pain.

Incidence ≥1%—Probably Causally Related
Gastrointestinal: Diarrhea (14%), dyspepsia (13%), abdominal pain (12%), constipation*, flatulence*, nausea*, positive stool guaiac*, dry mouth, gastritis, stomatitis, vomiting.
Central Nervous System: Dizziness*, headache*, fatigue, increased sweating, insomnia, nervousness, somnolence.
Dermatologic: Pruritus*, rash*.
Special Senses: Tinnitus*.
Miscellaneous: Edema*.

*Incidence of reported reaction between 3% and 9%. Reactions occurring in 1% to 3% of the patients are unmarked.

Incidence <1%—Probably Causally Related†
Gastrointestinal: Anorexia, jaundice, duodenal ulcer, dysphagia, gastric ulcer, gastroenteritis, gastrointestinal bleeding, increased appetite, liver function abnormalities, melena, *hepatic failure*.
Central Nervous System: Asthenia, agitation, anxiety, confusion, depression, malaise, paresthesia, tremor, vertigo.
Dermatologic: Bullous eruptions, photosensitivity, urticaria, pseudoporphyria cutanea tarda, *toxic epidermal necrolysis, erythema multiforme, Stevens-Johnson syndrome*.
Cardiovascular: Vasculitis.
Metabolic: Weight gain.
Respiratory: Dyspnea, *eosinophilic pneumonia, hypersensitivity pneumonitis, idiopathic interstitial pneumonitis*.
Genitourinary: Albuminuria, azotemia, *hyperuricemia, interstitial nephritis, nephrotic syndrome, vaginal bleeding, renal failure*.
Special Senses: Abnormal vision.
Hematologic/Lymphatic: *Thrombocytopenia*.
Hypersensitivity: *Anaphylactoid reaction, anaphylaxis,* angioneurotic edema.

†Adverse reactions reported only in worldwide postmarketing experience or in the literature, not seen in clinical trials, are considered rarer and are italicized.

Incidence <1%—Causal Relationship Unknown
Gastrointestinal: Bilirubinuria, duodenitis, eructation, gallstones, gingivitis, glossitis, pancreatitis, rectal bleeding.
Central Nervous System: Nightmares.
Dermatologic: Acne, alopecia.
Cardiovascular: Angina, arrhythmia, hypertension, myocardial infarction, palpitations, syncope, thrombophlebitis.
Respiratory: Asthma, cough.
Genitourinary: Dysuria, hematuria, impotence, renal stones.
Special Senses: Taste disorder.
Body as a Whole: Fever, chills.
Hematologic/Lymphatic: Anemia, leukopenia, granulocytopenia.
Metabolic/Nutritional: Hyperglycemia, hypokalemia, weight loss.

OVERDOSAGE

Symptoms following acute NSAIDs overdoses are usually limited to lethargy, drowsiness, nausea, vomiting, and epigastric pain, which are generally reversible with supportive care. Gastrointestinal bleeding can occur. Hypertension, acute renal failure, respiratory depression, and coma may occur, but are rare. Anaphylactoid reactions have been reported with therapeutic ingestion of NSAIDs, and may occur following an overdose.

Patients should be managed by symptomatic and supportive care following a NSAIDs overdose. There are no specific antidotes. Emesis and/or activated charcoal (60 to 100 grams in adults, 1 to 2 g/kg in children), and/or osmotic cathartic may be indicated in patients seen within 4 hours of ingestion with symptoms or following a large overdose (5 to 10 times the usual dose). Forced diuresis, alkalinization of urine, hemodialysis, or hemoperfusion may not be useful due to high protein binding.

There have been overdoses of up to 25 grams of RELAFEN reported with no long-term sequelae following standard emergency treatment (i.e., activated charcoal, gastric lavage, IV H_2-blockers, etc.).

DOSAGE AND ADMINISTRATION

Carefully consider the potential benefits and risks of RELAFEN and other treatment options before deciding to use RELAFEN. Use the lowest effective dose for the shortest duration consistent with individual patient treatment goals (see **WARNINGS**).

After observing the response to initial therapy with RELAFEN, the dose and frequency should be adjusted to suit an individual patient's needs.

Osteoarthritis and Rheumatoid Arthritis: The recommended starting dose is 1,000 mg taken as a single dose with or without food. Some patients may obtain more symptomatic relief from 1,500 mg to 2,000 mg per day. RELAFEN can be given in either a single or twice-daily dose. Dosages greater than 2,000 mg per day have not been studied. The lowest effective dose should be used for chronic treatment (see **WARNINGS, Renal Effects**). Patients weighing under 50 kg may be less likely to require dosages beyond 1,000 mg; therefore, after observing the response to initial therapy, the dose should be adjusted to meet individual patients' requirements.

HOW SUPPLIED

Tablets: Oval-shaped, film-coated: 500 mg–white, imprinted with the product name RELAFEN and 500, in bottles of 100, and in Single-Unit Packages of 100 (intended for institutional use only). 750 mg–beige, imprinted with the product name RELAFEN and 750, in bottles of 100, and in Single-Unit Packages of 100 (intended for institutional use only).

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) in well-closed container; dispense in light-resistant container.

500 mg 100's: NDC 0029-4851-20
500 mg SUP 100's: NDC 0029-4851-21
750 mg 100's: NDC 0029-4852-20

Medication Guide for

Non-Steroidal Anti-inflammatory Drugs (NSAIDs)

(See the end of this Medication Guide for a list of prescription NSAID medicines.)

What is the most important information I should know about medicines called Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)?

NSAID medicines may increase the chance of a heart attack or stroke that can lead to death. This chance increases:

- with longer use of NSAID medicines
- in people who have heart disease

NSAID medicines should never be used right before or after a heart surgery called a "coronary artery bypass graft (CABG)".

NSAID medicines can cause ulcers and bleeding in the stomach and intestines at any time during treatment.

Ulcers and bleeding:

- can happen without warning symptoms
- may cause death

The chance of a person getting an ulcer or bleeding increases with:

- taking medicines called "corticosteroids" and "anticoagulants"
- longer use
- smoking
- drinking alcohol
- older age
- having poor health

NSAID medicines should only be used:

- exactly as prescribed
- at the lowest dose possible for your treatment
- for the shortest time needed

What are Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)?

NSAID medicines are used to treat pain and redness, swelling, and heat (inflammation) from medical conditions such as:

- different types of arthritis
- menstrual cramps and other types of short-term pain

Who should not take a Non-Steroidal Anti-Inflammatory Drug (NSAID)?

Do not take an NSAID medicine:

- if you had an asthma attack, hives, or other allergic reaction with aspirin or any other NSAID medicine
- for pain right before or after heart bypass surgery

Tell your healthcare provider:

- about all of your medical conditions
- about all of the medicines you take. NSAIDs and some other medicines can interact with each other and cause serious side effects. **Keep a list of your medicines to show to your healthcare provider and pharmacist.**
- if you are pregnant. **NSAID medicines should not be used by pregnant women late in their pregnancy.**
- if you are breastfeeding. **Talk to your doctor.**

What are the possible side effects of Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)?

Serious side effects include:	**Other side effects include:**
• heart attack • stroke • high blood pressure • heart failure from body swelling (fluid retention) • kidney problems including kidney failure • bleeding and ulcers in the stomach and intestine • low red blood cells (anemia) • life-threatening skin reactions • life-threatening allergic reactions • liver problems including liver failure • asthma attacks in people who have asthma	• stomach pain • constipation • diarrhea • gas • heartburn • nausea • vomiting • dizziness

Get emergency help right away if you have any of the following symptoms:

• shortness of breath or trouble breathing • chest pain • weakness in one part or side of your body	• slurred speech • swelling of the face or throat

Stop your NSAID medicine and call your healthcare provider right away if you have any of the following symptoms:

• nausea • more tired or weaker than usual • itching • your skin or eyes look yellow • stomach pain • flu-like symptoms • vomit blood	• there is blood in your bowel movement or it is black and sticky like tar • unusual weight gain • skin rash or blisters with fever • swelling of the arms and legs, hands and feet

These are not all the side effects with NSAID medicines. Talk to your healthcare provider or pharmacist for more information about NSAID medicines.

Other information about Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)

- Aspirin is an NSAID medicine but it does not increase the chance of a heart attack. Aspirin can cause bleeding in the brain, stomach, and intestines. Aspirin can also cause ulcers in the stomach and intestines.
- Some of these NSAID medicines are sold in lower doses without a prescription (over-the-counter). Talk to your healthcare provider before using over-the-counter NSAIDs for more than 10 days.

NSAID medicines that need a prescription

Generic Name	**Tradename**
Celecoxib	Celebrex
Diclofenac	Cataflam, Voltaren, Arthrotec (combined with misoprostol)
Diflunisal	Dolobid
Etodolac	Lodine, Lodine XL
Fenoprofen	Nalfon, Nalfon 200
Flurbirofen	Ansaid
Ibuprofen	Motrin, Tab-Profen, Vicoprofen (combined with hydrocodone), Combunox (combined with oxycodone)
Indomethacin	Indocin, Indocin SR, Indo-Lemmon, Indomethagan
Ketoprofen	Oruvail
Ketorolac	Toradol
Mefenamic Acid	Ponstel
Meloxicam	Mobic
Nabumetone	Relafen
Naproxen	Naprosyn, Anaprox, Anaprox DS, EC-Naproxyn, Naprelan, Naprapac (copackaged with lansoprazole)
Oxaprozin	Daypro
Piroxicam	Feldene
Sulindac	Clinoril
Tolmetin	Tolectin, Tolectin DS, Tolectin 600

This Medication Guide has been approved by the U.S. Food and Drug Administration.

MG-RL:1

GlaxoSmithKline
Research Triangle Park, NC 27709

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