NABUMETONE- nabumetone tablet
Advanced Rx Pharmacy of Tennessee, LLC

Nabumetone 750mg Tablets

Boxed Warning

Cardiovascular Thrombotic Events

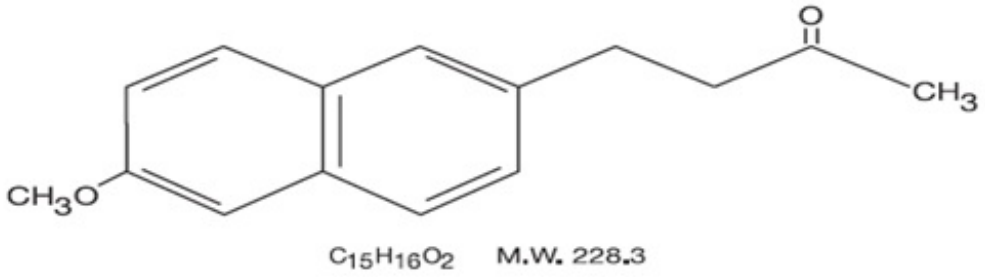
Nonsteroidal anti-inflammatory drugs (NSAIDs) cause an increased risk of serious cardiovascular thrombotic events, including myocardial infarction and stroke, which can be fatal. This risk may occur early in treatment and may increase with duration of use [see WARNINGS and PRECAUTIONS].
Nabumetone tablets are contraindicated in the setting of coronary artery bypass graft (CABG) surgery [see CONTRAINDICATIONS and WARNINGS].

Gastrointestinal Risk

• NSAIDs 1 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).

1Throughout this package insert, the term NSAID refers to a non-aspirin non-steroidal anti-inflammatory drug.

Description



$C_{15}H_{16}O_2$ M.W. 228.3

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

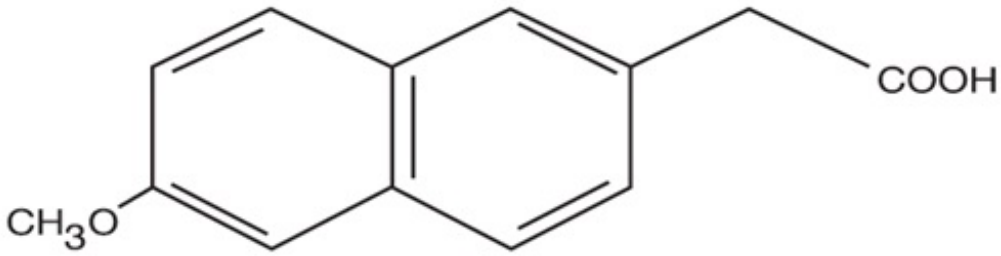
Nabumetone, USP is a white or almost white crystalline substance with a molecular weight of 228.3. It is nonacidic, freely soluble in acetone, sparingly soluble in alcohol and in methanol, practically insoluble in water. It has an n-octanol:phosphate buffer partition coefficient of 2400 at pH 7.4.

Each tablet, for oral administration contains either 500 mg or 750 mg of nabumetone, USP. In addition, each tablet contains the following inactive ingredients: hypromellose, microcrystalline cellulose, sodium lauryl sulfate, sodium starch glycolate, polyethylene glycol and titanium dioxide.

Clinical Pharmacology

Nabumetone 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.



6-methoxy-2-naphthylacetic acid (6MNA)

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 nabumetone, 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 nabumetone 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.

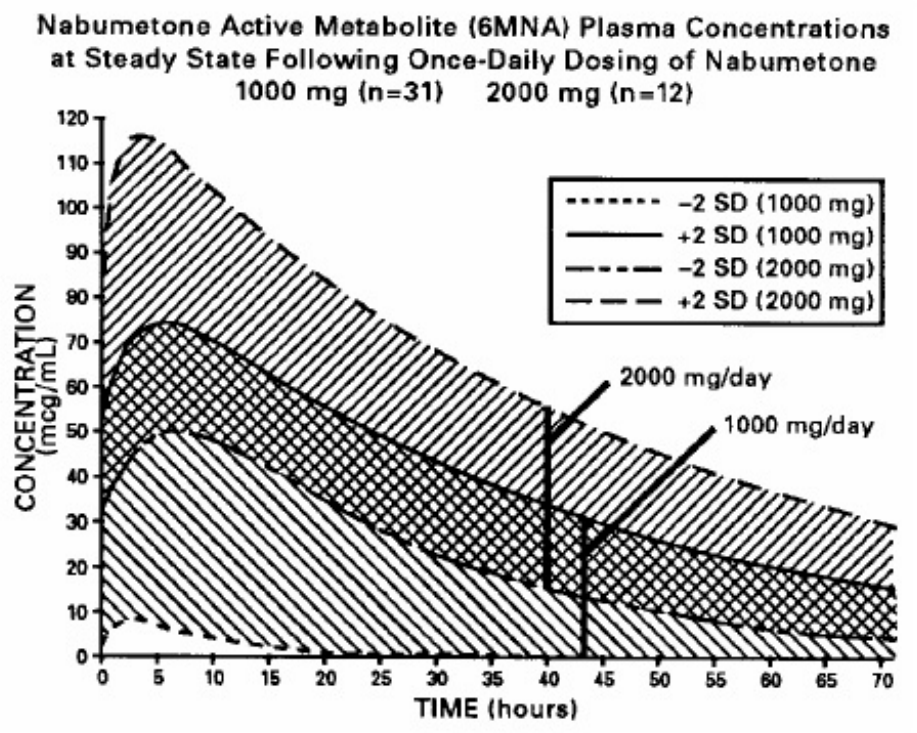
Coadministration with an aluminum-containing antacid had no significant effect on the bioavailability of 6MNA.

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 Nabumetone

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 nabumetone.



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 nabumetone generally is not necessary in patients with mild renal insufficiency (≥50 mL/min). Caution should be used in prescribing nabumetone to patients with moderate or severe renal insufficiency. The maximum starting doses of nabumetone 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: Nabumetone was compared to aspirin in inducing gastrointestinal blood loss. Food intake was not monitored. Studies utilizing 51Cr-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 nabumetone 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 nabumetone, 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 nabumetone daily or naproxen 250 mg or 500 mg twice daily for 3 to 12 weeks, treatment with nabumetone 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 nabumetone daily or piroxicam 10 mg to 20 mg for 7 to 10 days, there were fewer patients treated with nabumetone with endoscopically detected lesions. In 3 trials of a total of 47 patients on 1,000 mg of nabumetone 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 nabumetone 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 nabumetone 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 nabumetone 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 nabumetone 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, nabumetone 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 nabumetone 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. Nabumetone, 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, nabumetone has been used in combination with gold, d-penicillamine, and corticosteroids.

Patient Exposure in Clinical Trials of Osteoarthritis and Rheumatoid Arthritis:
In clinical trials with osteoarthritis and rheumatoid arthritis patients, most patients responded to nabumetone 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 Nabumetone in Osteoarthritis and Rheumatoid Arthritis

Dose of Nabumetone	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 Section

INDICATIONS AND USAGE

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

Nabumetone tablets, USP are indicated for relief of signs and symptoms of osteoarthritis and rheumatoid arthritis.

Contraindications

Nabumetone tablets are contraindicated in patients with known hypersensitivity to nabumetone or its excipients.

Nabumetone tablets 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).

Nabumetone tablets are contraindicated in the setting of coronary artery bypass graft (CABG) surgery [see WARNINGS].

Warnings and Precautions

CARDIOVASCULAR EFFECTS

Cardiovascular Thrombotic Events

Clinical trials of several COX-2 selective and nonselective NSAIDs of up to three years duration have shown an increased risk of serious cardiovascular (CV) thrombotic events, including myocardial infarction (MI) and stroke, which can be fatal. Based on available data, it is unclear that the risk for CV thrombotic events is similar for all NSAIDs. The relative increase in serious CV thrombotic events over baseline conferred by NSAID use appears to be similar in those with and without known CV disease or risk factors for CV disease. However, patients with known CV disease or risk factors had a higher absolute incidence of excess serious CV thrombotic events, due to their increased baseline rate. Some observational studies found that this increased risk of serious CV thrombotic events began as early as the first weeks of treatment. The increase in CV thrombotic risk has been observed most consistently at higher doses.

To minimize the potential risk for an adverse CV event in NSAID-treated patients, use the lowest effective dose for the shortest duration possible. Physicians and patients should remain alert for the development of such events, throughout the entire treatment course, even in the absence of previous CV symptoms. Patients should be informed about the 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, such as nabumetone, increases the risk of serious gastrointestinal (GI) events [see WARNINGS].

Status Post Coronary Artery Bypass Graft (CABG) Surgery

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. NSAIDs are contraindicated in the setting of CABG [see CONTRAINDICATIONS].

Post-MI Patients

Observational studies conducted in the Danish National Registry have demonstrated that patients treated with NSAIDs in the post-MI period were at increased risk of reinfarction, CV-related death, and all-cause mortality beginning in the first week of treatment. In this same cohort, the incidence of death in the first year post MI was 20 per 100 person years in NSAID-treated patients compared to 12 per 100 person years in non-NSAID exposed patients. Although the absolute rate of death declined somewhat after the first year post-MI, the increased relative risk of death in NSAID users persisted over at least the next four years of follow-up.

Avoid the use of nabumetone tablets in patients with a recent MI unless the benefits are expected to outweigh the risk of recurrent CV thrombotic events. If nabumetone tablets are used in patients with a recent MI, monitor patients for signs of cardiac ischemia.

Hypertension: NSAIDs, including nabumetone tablets, 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 nabumetone, 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.

Heart Failure and Edema

The Coxib and traditional NSAID Trialists' Collaboration meta-analysis of randomized controlled trials demonstrated an approximately two-fold increase in hospitalizations for heart failure in COX-2 selective-treated patients and nonselective NSAID-treated patients compared to placebo-treated patients. In a Danish National Registry study of patients with heart failure, NSAID use increased the risk of MI, hospitalization for heart failure, and death.

Additionally, fluid retention and edema have been observed in some patients treated with NSAIDs. Use of nabumetone may blunt the CV effects of several therapeutic agents used to treat these medical conditions [e.g., diuretics, ACE inhibitors, or angiotensin receptor blockers (ARBs)] [see DRUG INTERACTIONS].

Avoid the use of nabumetone tablets in patients with severe heart failure unless the benefits are expected to outweigh the risk of worsening heart failure. If nabumetone tablets are used in patients with severe heart failure, monitor patients for signs of worsening heart failure.

Gastrointestinal Effects—Risk of Ulceration, Bleeding, and Perforation: NSAIDs, including nabumetone tablets, 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 to 6 months, and in about 2 to 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 nabumetone (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 nabumetone 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 usually followed by recovery to the pretreatment state.

Advanced Renal Disease: No information is available from controlled clinical studies regarding the use of nabumetone tablets in patients with advanced renal disease. Therefore, treatment with nabumetone tablets is not recommended in these patients with advanced renal disease. If nabumetone tablets 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 nabumetone 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.

Anaphylactoid Reactions: As with other NSAIDs, anaphylactoid reactions may occur in patients without known prior exposure to nabumetone tablets. Nabumetone tablets 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 nabumetone tablets, 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.

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) has been reported in patients taking NSAIDs such as nabumetone tablets. Some of these events have been fatal or life-threatening. DRESS typically, although not exclusively, presents with fever, rash, lymphadenopathy, and/or facial swelling. Other clinical manifestations may include hepatitis, nephritis, hematological abnormalities, myocarditis, or myositis. Sometimes

symptoms of DRESS may resemble an acute viral infection. Eosinophilia is often present. Because this disorder is variable in its presentation, other organ systems not noted here may be involved. It is important to note that early manifestations of hypersensitivity, such as fever or lymphadenopathy, may be present even though rash is not evident. If such signs or symptoms are present, discontinue nabumetone tablets and evaluate the patient immediately.

Fetal Toxicity

Premature Closure of Fetal Ductus Arteriosus:

Avoid use of NSAIDs, including nabumetone tablets, in pregnant women at about 30 weeks gestation and later. NSAIDs including nabumetone tablets, increase the risk of premature closure of the fetal ductus arteriosus at approximately this gestational age.

Oligohydramnios/Neonatal Renal Impairment:

Use of NSAIDs, including nabumetone tablets, at about 20 weeks gestation or later in pregnancy may cause fetal renal dysfunction leading to oligohydramnios and, in some cases, neonatal renal impairment. These adverse outcomes are seen, on average, after days to weeks of treatment, although oligohydramnios has been infrequently reported as soon as 48 hours after NSAID initiation.

Oligohydramnios is often, but not always, reversible with treatment discontinuation. Complications of prolonged oligohydramnios may, for example, include limb contractures and delayed lung maturation. In some postmarketing cases of impaired neonatal renal function, invasive procedures such as exchange transfusion or dialysis were required.

If NSAID treatment is necessary between about 20 weeks and 30 weeks gestation, limit nabumetone tablets use to the lowest effective dose and shortest duration possible. Consider ultrasound monitoring of amniotic fluid if nabumetone tablets treatment extends beyond 48 hours. Discontinue nabumetone tablets if oligohydramnios occurs and follow up according to clinical practice [see PRECAUTIONS; PREGNANCY].

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 nabumetone 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 nabumetone reported with no long-term sequelae following standard emergency treatment (i.e., activated charcoal, gastric lavage, IV H 2-blockers, etc.).

Dosage and Administration Section

DOSAGE AND ADMINISTRATION

Carefully consider the potential benefits and risks of nabumetone tablets and other treatment options before deciding to use nabumetone tablets. 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 nabumetone tablets, 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. Nabumetone tablets 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/Storage and Handling

Nabumetone Tablets, USP:

Nabumetone tablets USP, 750 mg are white colored, oval shaped, biconvex, film coated tablets, debossed with ‘SG’ on one side ‘466’ on other side.

Bottles of 30 Tablets NDC: 80425-0104-01

Bottles of 60 Tablets NDC: 80425-0104-02

Bottles of 90 Tablets NDC: 80425-0104-03

Store at 20° to 25°C (68° to 77°F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature].

Dispense in tight, light-resistant container as defined in the USP, with a child-resistant closure (as required).

Rx Only

Manufactured by:
ScieGen Pharmaceuticals, Inc.
Hauppauge, NY 11788

Rev: 4/2021

Medication Guide Section

MEDICATION GUIDE

Medication Guide

for Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)

What is the most important information I should know about medicines called Nonsteroidal Antiinflammatory Drugs (NSAIDs)?

NSAIDs can cause serious side effects, including:

• Increased risk of a heart attack or stroke that can lead to death. This risk may happen early in treatment and may increase:

with increasing doses of NSAIDs
with longer use of NSAIDs

Do not take NSAIDs right before or after a heart surgery called a “coronary artery bypass graft (CABG)."

Avoid taking NSAIDs after a recent heart attack, unless your healthcare provider tells you to. You may have an increased risk of another heart attack if you take NSAIDs after a recent heart attack.

• Increased risk of bleeding, ulcers, and tears (perforation) of the esophagus (tube leading from the mouth to the stomach), stomach and intestines:

anytime during use
without warning symptoms
that may cause death

The risk of getting an ulcer or bleeding increases with:

past history of stomach ulcers, or stomach or intestinal bleeding with use of NSAIDs
taking medicines called “corticosteroids”, “anticoagulants”, “SSRIs”, or “SNRIs”
increasing doses of NSAIDs
longer use of NSAIDs
smoking

drinking alcohol
older age
poor health
advanced liver disease
bleeding problems

NSAIDs should only be used:

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

What are NSAIDs?

NSAIDs 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 NSAIDs?

Do not take NSAIDs:

• if you have had an asthma attack, hives, or other allergic reaction with aspirin or any other NSAIDs.

• right before or after heart bypass surgery.

Before taking NSAIDS, tell your healthcare provider about all of your medical conditions, including if you:

• have liver or kidney problems

• have high blood pressure

• have asthma

• are pregnant or plan to become pregnant. Talk to your healthcare provivder if you are considering taking NSAIDs during pregnancy. You should not take NSAIDs after 29 weeks of pregnancy.

• are breastfeeding or plan to breast feed.

Tell your healthcare provider about all of the medicines you take, including prescription or over-the-counter medicines, vitamins or herbal supplements. NSAIDs and some other medicines can interact with each other and cause serious side effects. Do not start taking any new medicine without talking to your healthcare provider first.

What are the possible side effects of NSAIDs?

NSAIDs can cause serious side effects, including:

See “What is the most important information I should know about medicines called Nonsteroidal Antiinflammatory Drugs (NSAIDs)?

• new or worse high blood pressure

• heart failure

• liver problems including liver failure

• kidney problems including kidney failure

• low red blood cells (anemia)

• life-threatening skin reactions

• life threatening allergic reactions

• Other side effects of NSAIDs include: stomach pain, constipation, diarrhea, gas, heartburn, nausea, vomiting, and dizziness.

Get emergency help right away if you get 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 taking your NSAID and call your healthcare provider right away if you get any of the following symptoms:

• nausea

• more tired or weaker than usual

• diarrhea

• itching

• your skin or eyes look yellow

• indigestion or 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, legs, hands and feet

If you take too much of your NSAID, call your healthcare provider or get medical help right away.

These are not all the possible side effects of NSAIDs. For more information, ask your healthcare provider or pharmacist about NSAIDs.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

Other information about NSAIDs

• Aspirin is an NSAID 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 NSAIDs 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.

General information about the safe and effective use of NSAIDs

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use NSAIDs for a condition for which it was not prescribed. Do not give NSAIDs to other people, even if they have the same symptoms that you have. It may harm them.

If you would like more information about NSAIDs, talk with your healthcare provider. You can ask your pharmacist or healthcare provider for information about NSAIDs that is written for health professionals.

For more information, call 1-855-724-3436.

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

Rx Only

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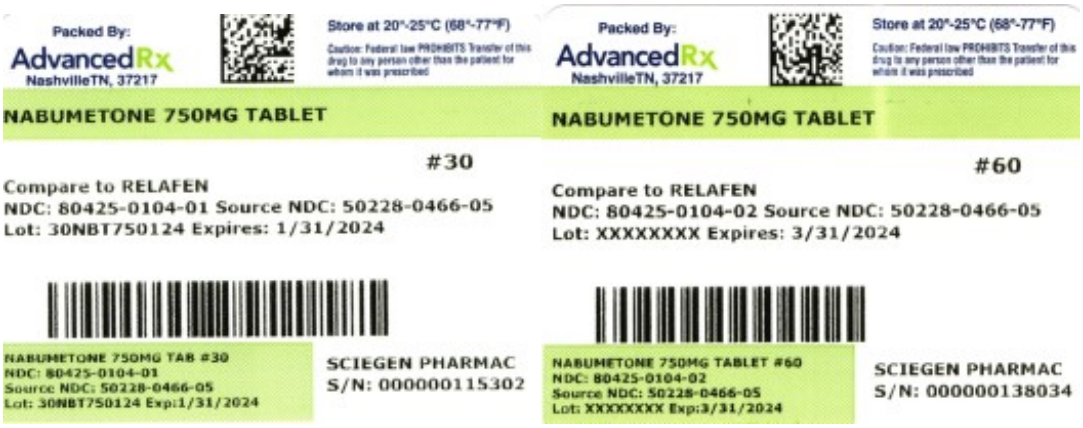
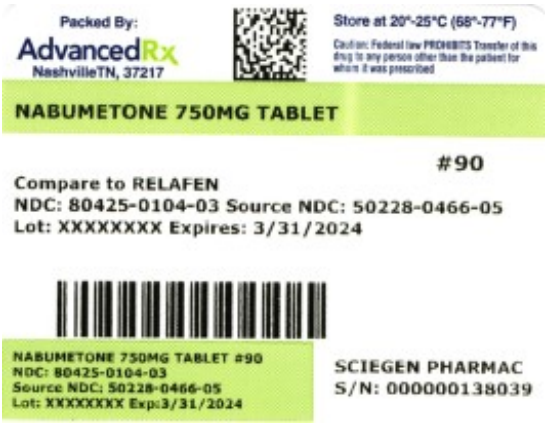
Principal Display Panel





NABUMETONE

nabumetone tablet

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:80425-0104(NDC:50228-466)
Route of Administration	ORAL		

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
NABUMETONE (UNII: LW0TIW155Z) (NABUMETONE - UNII:LW0TIW155Z)	NABUMETONE	750 mg

Product Characteristics			
Color	white	**Score**	no score
Shape	OVAL	**Size**	19mm
Flavor		**Imprint Code**	SG;466
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:80425-0104-1	30 in 1 BOTTLE; Type 0: Not a Combination Product	06/26/2019	
2	NDC:80425-0104-2	60 in 1 BOTTLE; Type 0: Not a Combination Product	04/07/2023	
3	NDC:80425-0104-3	90 in 1 BOTTLE; Type 0: Not a Combination Product	04/07/2023	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA078420	06/26/2019	

Labeler - Advanced Rx Pharmacy of Tennessee, LLC (117023142)

Establishment

Name	Address	ID/FEI	Business Operations
Advanced Rx Pharmacy of Tennessee, LLC		117023142	repack(80425-0104)

Revised: 4/2023 Advanced Rx Pharmacy of Tennessee, LLC