CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75-189

APPROVED DRAFT LABELING

R 1234 67 12

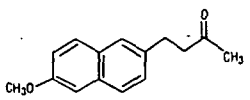
1015 **NABUMETONE TABLETS**

APPROVED

MAY 26 2000

DESCRIPTION

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



M.W. 228.3

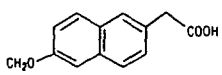
Nabumetone is a white to off-white crystalline substance. It is nonacidic and practically insoluble in water, but soluble in alcohol and most organic solvents. It has an n-octanol:phosphate buffer partition coefficient of 2400 at pH 7.4.

Each tablet, for oral administration, contains 500 mg of nabumetone. In addition, each tablet contains the following inactive ingredients: colloidal silicon dioxide, hydroxypropyl methylcellulose, microcrystalline cellulose, polyethylene glycol, sodium lauryl sulphate, sodium starch glycolate, talc, and titanium dioxide.

CLINICAL PHARMACOLOGY

Nabumetone is a nonsteroidal anti-inflammatory drug (NSAID) that exhibits anti-inflammatory, analgesic and antipyretic properties in pharmacologic studies. As with other nonsteroidal 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 1000 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 protains. The free fraction is dependent on total concentration of 6MNA and is proportional to dose over the range of 1000 mg to 2000 mg. It is 0.2% to 0.3% at concentrations typically achieved following administration of nabumetone 1000 mg and is approximately 0.6% to 0.8% of the total concentrations at steady state following daily administration of 2000 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.

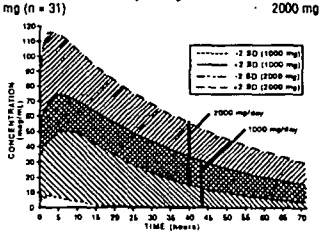
Table 1. Mean pharmacokinetic parameters of nabumetone active metabolite (6MNA) at steady state following oral administration of 1000 mg or 2000 mg doses of nabumetone

Abbreviation (units)	Young Adults Mean ± SD 1000 mg n = 31	Young Adults Mean ± SD 2000 mg n = 12	Elderly Mean ± SD 1000 mg n = 27
t_{max} (hours)	3.0 (1.0 to 12.0)	2.5 (1.0 to 8.0)	4.0 (1.0 to 10.0)
$t_{1/2}$(hours)	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 1000 mg to 2000 mg doses to steady state. The crosshatched area represents the expected overlap in plasma concentrations due to intersubject variation following oral administration of 1000 mg to 2000 mg of nabumetone.

Nabumetone Active Metabolite (6MNA) Plasma Concentrations at Steady State Following Once-Daily Dosing of Nabumetone

1000 mg (n = 31) 2000 mg (n = 12)



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%

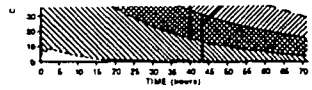
Following oral administration of dosages of 1000 mg to 2000 mg to steady state, the mean plasma clearance of 6MNA is 20 to 30 mL/min. and the elimination half-life is approximately 24 hours.

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 studies of patients with renal insufficiency, the mean terminal half-life of 6MNA was increased in patients with severe renal dysfunction (creatinine clearance <30 mL/min./1.73 m^2). In patients undergoing hemodialysis, steady-state plasma concentrations of the active metabolite were similar



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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 ^{51}Cr-tagged red blood cells in healthy males showed no difference in fecal blood loss after 3 or 4 weeks' administration of nabumetone 1000 mg or 2000 mg daily when compared to either placebo-treated or nontreated subjects. In contrast, aspirin 3600 mg daily produced an increase in fecal blood loss when compared to the nabumetone-treated, placebo-treated or nontreated subjects. 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 nabumetone 1000 mg daily or naproxen 250 mg or 500 mg twice daily for 3 to 12 weeks, nabumetone treatment resulted in fewer patients with endoscopically detected lesions (>3mm). In 2 trials a total of 101 patients on nabumetone 1000 mg or 2000 mg daily or piroxicam 10 mg to 20 mg for 7 to 10 days, there were fewer nabumetone patients with endoscopically detected lesions. In 3 trials of a total of 47 patients on nabumetone 1000 mg 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 nabumetone 1000 mg/day to ibuprofen 2400 mg/day and ibuprofen 2400 mg/day plus misoprostol 800 mcg/day. The results showed that patients treated with nabumetone had a lower number of endoscopically detected lesions (>5mm) 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, nabumetone 1000 mg 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 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 1000 mg/day administered at night was comparable to naproxen 500 mg/day and to aspirin 3600 mg/day.

Rheumatoid Arthritis
The use of nabumetone in relieving the signs and symptoms of rheumatoid arthritis 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 1000 mg/day administered at night was comparable to naproxen 500 mg/day and to aspirin 3600 mg/day.

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

INDIVIDUALIZATION OF DOSING
There is considerable interpatient variation in response to nabumetone. Therapy is usually initiated at a nabumetone dose of 1000 mg daily, then adjusted, if needed, based on clinical response.

In clinical trials with osteoarthritis and rheumatoid arthritis patients, most patients responded to nabumetone in doses of 1000 mg/day administered nightly; total daily dosages up to 2000 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 U.S. clinical trials:

Table 2. Clinical double-blind and open-labelled trials of nabumetone in osteoarthritis and rheumatoid arthritis

Nabumetone Dose	Number of Patients OA	Number of Patients RA	Mean/Mode Duration of Treatment (yrs.) OA	Mean/Mode Duration of Treatment (yrs.) RA
500 mg	17	6	0.4/-	0.2/-
1000 mg	917	701	1.2/1	1.4/1
1500 mg	645	224	2.3/1	1.7/1
2000 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 1000 mg. Therefore, after observing the response to initial therapy, the dose should be adjusted to meet individual patients' requirements.

INDICATIONS AND USAGE
Nabumetone tablets are indicated for acute and chronic treatment of signs and symptoms of osteoarthritis and rheumatoid arthritis.

CONTRAINDICATIONS
Nabumetone is contraindicated in patients who have previously exhibited hypersensitivity to it.

Nabumetone is contraindicated in patients in whom nabumetone, aspirin or other NSAIDs induce asthma, urticaria or other allergic-type reactions. Fatal asthmatic reactions have been reported in such patients receiving NSAIDs.

WARNINGS
Risk of G.I. Ulceration, Bleeding and Perforation with NSAID Therapy
Serious gastrointestinal toxicity such as bleeding, ulceration and perforation can occur at any time, with or without warning symptoms, in patients treated chronically with NSAID therapy. Although minor upper gastrointestinal problems, such as dyspepsia, are common, usually developing early in therapy, physicians should remain alert for ulceration and bleeding in patients treated chronically with NSAIDs even in the absence of previous G.I. tract symptoms.

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. Physicians should inform patients about the signs and symptoms of serious G.I. toxicity and what steps to take if they occur. In patients

with active peptic ulcer, physicians must weigh the benefits of nabumetone therapy against possible hazards, institute an appropriate ulcer treatment regimen and monitor the patients' progress carefully.

Studies to date have not identified any subset of patients not at risk of developing peptic ulceration and bleeding. Except for a prior history of serious G.I. events and other risk factors known to be associated with peptic ulcer disease, such as alcoholism, smoking, etc., no risk factors (e.g., age, sex) have been associated with increased risk. Elderly or debilitated patients seem to tolerate ulceration or bleeding less well than other individuals and most spontaneous reports of fatal G.I. events are in this population.

High doses of any NSAID probably carry greater risk of these reactions, although controlled clinical trials showing this do not exist in most cases. In considering the use of relatively large doses (within the recommended dosage range), sufficient benefit should be anticipated to offset the potential increased risk of G.I. toxicity.

PRECAUTIONS

General

Renal Effects

As a class, NSAIDs have been associated with renal papillary necrosis and other abnormal renal pathology during long-term administration to animals.

A second form of renal toxicity often associated with NSAIDs is seen in patients with conditions leading to a reduction in renal blood flow or blood volume, where renal prostaglandins have a supportive 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.

Because nabumetone undergoes extensive hepatic metabolism, no adjustment of nabumetone dosage is generally necessary in patients with 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, Special Studies**). 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.

Hepatic Function

As with other NSAIDs, borderline elevations of one or more liver function tests may occur in up to 15% of patients. These abnormalities may progress, may remain essentially unchanged, or may return to normal with continued therapy. The ALT (SGPT) test is probably the most sensitive indicator of liver dysfunction. Meaningful (3 times the upper limit of normal) elevations of ALT (SGPT) or AST (SGOT) have occurred in controlled clinical trials of nabumetone in less than 1% of patients. 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 nabumetone therapy. Severe hepatic reactions, including jaundice and fatal hepatitis, have been reported with other NSAIDs. Although such reactions are rare, if abnormal liver tests persist or worsen, if clinical signs and symptoms consistent with liver disease develop, or if systemic manifestations occur (*e.g.*, eosinophilia, rash, etc.), nabumetone should be discontinued. Because nabumetone's biotransformation to 6MNA is dependent upon hepatic function, the biotransformation could be decreased in patients with severe hepatic dysfunction. Therefore, nabumetone should be used with caution in patients with severe hepatic impairment (see **Pharmacokinetics, *Hepatic Impairment***).

Fluid Retention and Edema

Fluid retention and edema have been observed in some patients taking nabumetone. Therefore, as with other NSAIDs, nabumetone should be used cautiously in patients with a history of congestive heart failure, hypertension or other conditions predisposing to fluid retention.

Photosensitivity

Based on U.V. light photosensitivity testing, nabumetone may be associated with more reactions to sun exposure than might be expected based on skin tanning types.

Information for Patients

Nabumetone, like other drugs of its class, is not free of side effects. The side effects of these drugs can cause discomfort and, rarely, there are more serious side effects, such as gastrointestinal bleeding, which may result in hospitalization and even fatal outcome.

NSAIDs are often essential agents in the management of arthritis, but they also may be commonly employed for conditions which are less serious. Physicians may wish to discuss with their patients the potential risks (see **WARNINGS, PRECAUTIONS** and **ADVERSE REACTIONS**) and likely benefits of NSAID treatment, particularly when the drugs are used for less serious conditions where treatment without NSAIDs may represent an acceptable alternative to both the patient and the physician.

Laboratory Tests

Because severe G.I. tract ulceration and bleeding can occur without warning symptoms, physicians should follow chronically treated patients for signs and symptoms of ulceration and bleeding, and should inform them of the importance of this follow-up (see **WARNINGS, Risk of G.I. Ulceration, Bleeding and Perforation with NSAID Therapy**).

Drug Interactions

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 nabumetone 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 **Pharmacokinetics**).

Carcinogenesis, Mutagenesis

In two-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 nabumetone 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 (1888 mg/m^2) before mating.

Pregnancy: Teratogenic Effects. Pregnancy Category C.

Nabumetone did not cause any teratogenic effect in rats given up to 400 mg/kg (2360 mg/m^2) and in rabbits up to 300 mg/kg (3540 mg/m^2) orally. However, increased post-implantation loss was observed in rats at 100 mg/kg (590 mg/m^2) orally and at higher doses (equal to the average human exposure to 6MNA at the maximum recommended human dose). There are no adequate, well-controlled studies in pregnant women. This drug should be used during pregnancy only if clearly needed.

Because of the known effect of prostaglandin-synthesis-inhibiting drugs on the human fetal cardiovascular system (closure of ductus arteriosus), use of nabumetone during the third trimester of pregnancy is not recommended.

Labor and Delivery

The effects of nabumetone on labor and delivery in women are not known. As with other drugs known to inhibit prostaglandin synthesis, an increased incidence of dystocia and delayed parturition occurred in rats treated throughout pregnancy.

Nursing Mothers

Nabumetone is not recommended for use in nursing mothers because of the possible adverse effects of prostaglandin-synthesis-inhibiting drugs on neonates. It is not known whether nabumetone or its metabolites are excreted in human milk; however, 6MNA is excreted in the milk of lactating rats.

Pediatric Use

Nabumetone is not recommended for use in pediatric patients because the safety and efficacy in pediatric patients have not been established.

Geriatric Use

Of the 1,677 patients in U.S. clinical studies who were treated with nabumetone, 411 patients (24%) were 65 years of age or older; 22 patients (1%) were 75 years of age 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-U.S. postmarketing surveillance study of 10,800 nabumetone patients, of whom 4,577 patients (42%) were 65 years of age 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 U.S. clinical studies.

Of the 1,677 patients who received nabumetone during U.S. 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. Over 300 patients have been treated for 5 years or longer.

The most frequently reported adverse reactions were related to the gastrointestinal tract. They were 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, cholestatic jaundice, duodenal ulcer, dysphagia, gastric ulcer, gastroenteritis, gastrointestinal bleeding, increased appetite, liver function abnormalities, melena.

Central Nervous System

Asthenia, agitation, anxiety, confusion, depression, malaise, paresthesia, tremor, vertigo.

Dermatologic

Bullous eruptions, photosensitivity, urticaria, pseudoporphyria cutanea tarda, *toxic epidermal necrolysis*.

Cardiovascular

Vasculitis.

Metabolic

Weight gain.

Central Nervous System
Dizziness*, headache*, fatigue, increased sweating, insomnia, nervousness, somnolence.

Dermatologic
Pruritus*, rash*.

Special Senses
Tinnitus*.

Miscellaneous
Edema*.

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Incidence <1%--Probably Causally Related†

Gastrointestinal
Anorexia, cholestatic jaundice, duodenal ulcer, dysphagia, gastric ulcer, gastroenteritis, gastrointestinal bleeding, increased appetite, liver function abnormalities, melena.

Central Nervous System
Asthenia, agitation, anxiety, confusion, depression, malaise, paresthesia, tremor, vertigo.

Dermatologic
Bullous eruptions, photosensitivity, urticaria, pseudoporphyria cutanea tarda, *toxic epidermal necrolysis.*

Cardiovascular
Vasculitis.

Metabolic
Weight gain.

Respiratory
Dyspnea, *eosinophilic pneumonia, hypersensitivity pneumonitis.*

Genitourinary
Albuminuria, azotemia, *hyperuricemia, interstitial nephritis, vaginal bleeding.*

Special Senses
Abnormal vision.

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, *erythema multiforme, Stevens-Johnson Syndrome.*

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, thrombocytopenia.

Metabolic/Nutritional
Hyperglycemia, hypokalemia, weight loss.

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OVERDOSAGE

Since only 1 case of nabumetone overdose has been reported, the experience is limited. If acute overdose occurs, it is recommended that the stomach be emptied by vomiting or lavage and general supportive measures be instituted, as necessary. In addition, the use of activated charcoal, up to 60 grams, may effectively reduce nabumetone absorption. Coadministration of nabumetone with charcoal to man has resulted in an 80% decrease in maximum plasma concentrations of the active metabolite.

The 1 overdose occurred in a 17-year-old female patient who had a history of abdominal pain and was hospitalized for increased abdominal pain following ingestion of 30 nabumetone tablets (15 grams total). Stools were negative for occult blood and there was no fall in serum hemoglobin concentration. The patient had no other symptoms. She was given an H_2-receptor antagonist and discharged from the hospital without sequelae.

DOSAGE AND ADMINISTRATION

Osteoarthritis and Rheumatoid Arthritis

The recommended starting dose is 1000 mg taken as a single dose with or without food. Some patients may obtain more symptomatic relief from 1500 mg to 2000 mg per day. Nabumetone tablets can be given in either a single or twice-daily dose. Dosages over 2000 mg per day have not been studied. The lowest effective dose should be used for chronic treatment.

HOW SUPPLIED

Nabumetone Tablets, 500 mg are white, oval-shaped, unscored, film coated tablets debossed with the numbers "93" on one face of the tablet and "15" on the other. They are available in bottles of 60, 100 and 1000.

Store at controlled room temperature 15°-30°C (59°-86°F).

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

Manufactured By:
TEVA PHARMACEUTICAL IND. LTD.
Jerusalem, 91010, Israel

Manufactured For:
TEVA PHARMACEUTICALS USA
Sellersville, PA 18960

Rev. C 4/2000

NABUMETONE Tablets 500 mg

Each tablet contains:
Nabumetone 500 mg

℞ only

1000 TABLETS

APPROVED MAY 26, 2000

TEVA

l Dosage: See package insert for full prescribing
nation.

at controlled room temperature
) 30°C (59° to 86°F).

nse in a tight, light-resistant container as defined in
SP, with a child-resistant closure (as required).

THIS AND ALL MEDICATIONS OUT OF THE REACH OF
)REN. TP Rev. A 3/98

factured By:
PHARMACEUTICAL IND. LTD.
alem, 91010, Israel
factured For:
PHARMACEUTICALS USA
sville, PA 18960

N 3 0093-1015-10 5

NDC 0093-1016-10

NABUMETONE Tablets 750 mg

Each tablet contains:
Nabumetone 750 mg

℞ only

1000 TABLETS

APPROVED MAY 26, 2000

TEVA

Usual Dosage: See package insert for full prescribing information.

Store at controlled room temperature
15° to 30°C (59° to 86°F).

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

KEEP THIS AND ALL MEDICATIONS OUT OF THE REACH OF CHILDREN. TP Rev. A 3/98

Manufactured By:
TEVA PHARMACEUTICAL IND. LTD.
Jerusalem, 91010, Israel
Manufactured For:
TEVA PHARMACEUTICALS USA
Sellersville, PA 18960

N 3 0093-1016-10 2

NDC 0093-1016-01

NABUMETONE Tablets 750 mg

Each tablet contains:
Nabumetone 750 mg

℞ only

APPROVED

100 TABLETS

TEVA

Usual Dosage: See package insert for full prescribing information.

Store at controlled room temperature
15° to 30°C (59° to 86°F).

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

KEEP THIS AND ALL MEDICATIONS OUT OF THE REACH OF CHILDREN. TP Rev. A 3/98

Manufactured By:
TEVA PHARMACEUTICAL IND. LTD.
Jerusalem, 91010, Israel
Manufactured For
TEVA PHARMACEUTICALS USA
Sellersville, PA 18960

N 3 0093-1016-01 0

NDC 0093-1016-10

NABUMETONE Tablets 750 mg

Each tablet contains:
Nabumetone 750 mg

APPROVED

℞ only

1000 TABLETS

TEVA

Usual Dosage: See package insert for full prescribing information.

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Jerusalem, 91010, Israel
Manufactured For:
TEVA PHARMACEUTICALS USA
Sellersville, PA 18960

N 0093-1016-10 2

NDC 0093-1015-10

NABUMETONE Tablets 500 mg

Each tablet contains:
Nabumetone 500 mg

MAY 26 2000

APPROVED

℞ only

1000 TABLETS

TEVA

Usual Dosage: See package insert for full prescribing information.

Store at controlled room temperature
15° to 30°C (59° to 86°F).

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

KEEP THIS AND ALL MEDICATIONS OUT OF THE REACH OF CHILDREN.

TP Rev. A 3/98

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TEVA PHARMACEUTICAL IND. LTD.
Jerusalem, 91010, Israel
Manufactured For:
TEVA PHARMACEUTICALS USA
Sellersville, PA 18960

N 0093-1015-10 5

NDC 0093-1016-01

NABUMETONE Tablets 750 mg

Each tablet contains:
Nabumetone 750 mg

APPROVED

℞ only

100 TABLETS

TEVA

Usual Dosage: See package insert for full prescribing information.

Store at controlled room temperature
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TP Rev. A 3/98

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Jerusalem, 91010, Israel
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TEVA PHARMACEUTICALS USA
Sellersville, PA 18960

N 0093-1016-01 0

NDC 0093-1015-01

NABUMETONE
Tablets
500 mg

APPROVED

Each tablet contains:
Nabumetone 500 mg

2000

℞ only

26

100 TABLETS

TEVA

Usual Dosage: See package insert for full prescribing information.

Store at controlled room temperature 15° to 30°C (59° to 86°F).

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

KEEP THIS AND ALL MEDICATIONS OUT OF THE REACH OF CHILDREN.

TP Rev. A 3/98

Manufactured By:
TEVA PHARMACEUTICAL IND. LTD.
Jerusalem, 91010, Israel

Manufactured For
TEVA PHARMACEUTICALS USA
Sellersville, PA 18960

N 3 0093-1015-01 3

NDC 0093-1015-06

NABUMETONE
Tablets
500 mg

APPROVED

Each tablet contains:
Nabumetone 500 mg

℞ only

60 TABLETS

TEVA

Usual Dosage: See package insert for full prescribing information.

Store at controlled room temperature 15° to 30°C (59° to 86°F).

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

KEEP THIS AND ALL MEDICATIONS OUT OF THE REACH OF CHILDREN.

TP Rev. A 3/98

Manufactured By:
TEVA PHARMACEUTICAL IND. LTD.
Jerusalem, 91010, Israel

Manufactured For
TEVA PHARMACEUTICALS USA
Sellersville, PA 18960

N 3 0093-1015-06 8

NDC 0093-1016-06

NABUMETONE
Tablets
750 mg

2000

Each tablet contains:
Nabumetone 750 mg

℞ only

APPROVED

60 TABLETS

TEVA

Usual Dosage: See package insert for full prescribing information.

Store at controlled room temperature 15° to 30°C (59° to 86°F).

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Jerusalem, 91010, Israel

Manufactured For
TEVA PHARMACEUTICALS USA
Sellersville, PA 18960

N 3 0093-1016-06 5